HEALTH TECHNOLOGY REVIEW

The Efficacy and Effectiveness of Sustained Release Oral Nitroglycerin in Comparison to Regular Delivery Isosorbide Dinitrate for the Prophylactic Treatment of Stable Angina Pectoris

BCOHTA 94:1T

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September 1994
FOREWORD

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1. BACKGROUND AND SIGNIFICANCE

The British Columbia Pharmacare Program has recently reconsidered its policy of reimbursing eligible patients, primarily senior citizens, for the cost of all prescription and many non-prescription drugs. As a result, the exclusive right of prescribing physicians to determine which drugs are suitable for reimbursement has been challenged. It is towards developing a more discriminating formulary that this policy is directed.

Developing a more discriminating formulary requires not only a great deal of effort over an extended period of time but also certain types of evidence. The evidence needed - termed relative efficacy - would be from randomized controlled trials that compare drugs with one another. Relative efficacy studies have not previously been required for drug licensing or distribution and, therefore, are less commonly found in the literature. Instead, the literature is dominated by the required absolute efficacy, or placebo controlled studies. The paucity of relative efficacy evidence, especially for older drugs, leads to difficulties in the formulary review process as will be illustrated in this report.

One of the concerns of the Drug Utilization Review Committee, which Pharmacare mandated to begin the formulary review process, was the utilization pattern found for organic nitrates - drugs used for the treatment of myocardial ischemic pain, termed angina pectoris. The Committee noted that despite the wide variety of products available for angina prophylaxis, approximately one half of the annual provincial Pharmacare expenditure for this category of drugs - totaling 10.1 million dollars in 1993* - was spent on sustained release forms of oral nitroglycerin (SR-NG). This preparation costs approximately ten times more per usual dose regimen than generic, regular release Isosorbide dinitrate (ISDN). They also noted that, in Saskatchewan and Ontario, SR-NG has never been listed in provincially funded formularies, and in Manitoba, this product was recently delisted. The Committee therefore asked whether scientific evidence supported the use of SR-NG oral tablets in comparison to cheaper oral tablet alternatives. While noting transdermal nitrates as additional alternatives to SR-NG within the nitrate category of drugs, the committee explicitly did not wish to examine the broader question of transdermal nitrates at this time. In addition, the committee did not wish to consider other categories of cardiac drugs also used for angina prophylaxis.

* Includes the wholesale acquisition cost of drugs and dispensing fee (Source: Pharmacare Therapeutic Class Analysis 1993, B.C. Ministry of Health).
2. RESEARCH QUESTION

The primary research question centers on whether any evidence, and if so what kind of evidence, supports use of SR-NG compared to regular release ISDN for the prophylactic treatment of stable angina pectoris*. Other indications for oral nitrate use (ie. during cardiac procedures, in the acute post-myocardial infarction period) are not under examination. Also not examined are transdermally delivered nitrates, products also designed for angina prophylaxis.

In the appropriate dosage**, all nitrates, including oral nitrates such as ISDN and SR-NG, are widely accepted as safe, effective anti-anginal agents1-2. Our assessment, therefore, is focused on the evidence concerning relative rather than absolute efficacy and effectiveness of these two agents.

Comparing ISDN and SR-NG is appropriate since reliable and valid clinical end-points exists for this category of drugs both for efficacy, namely characteristic electrocardiographic changes and patient symptom development during graded exercise testing3-5; and for effectiveness, using a quality of life research tool designed for assessment of anti-anginal therapy6-7.

3. DEFINITIONS

Oral means swallowed tablets, as opposed to tablets retained sublingually or buccally.

Efficacy refers to patient benefit under ideal circumstances, such as correct dosage given to correctly diagnosed patients and their responses measured both subjectively and objectively using valid and standardized protocols.

Effectiveness refers to patient benefit during less rigorous circumstances of daily life when the condition under examination is less carefully isolated in an experimental format and the treatment is less rigorously applied. The measurements used to determine effectiveness vary from patient accounts to questionnaires to more rigorous comparisons with gold standard therapies.

* Note: Sublingual and buccal tablets, as well as oral sprays are used in the treatment of acute angina as opposed to angina prophylaxis. They are not considered in this review.

** See "Tolerance" section, 7.1.
4. TECHNOLOGY DESCRIPTION

Oral nitrates are long-standing drugs used both alone and in combination with other agents for patients with ischemic heart disease. The advantages of these drugs include established efficacy, known physiological mechanism of action, minimal side effects, and relative low cost.

The principle mechanism of action for oral nitrates are similar to all other nitrates. They act on the myocardium through preload* reduction by venodilatation, as well as dilating stenotic and nonstenotic coronary arteries. Ischemia is thus prevented by both improving oxygen supply to the myocardium and reducing cardiac workload. The effect on preload is considered the predominant action by which nitrates relieve angina. Nitrates also exert a smaller, less significant action in dilating arterioles thereby slightly reducing afterload**.

ISDN and SR-NG, the two oral nitrates compared here, while differing in both chemical structure and delivery form as well as initial metabolism, act through a common final physiological pathway. This common final mechanism justifies their comparison in this report.

Isosorbide dinitrate, synthesized in 1938, remains as the world's most commonly used oral nitrate. In the appropriate dosage, it is widely accepted as highly effective in the prophylaxis of myocardial ischemic pain. ISDN is marketed in various dosage strengths and is available in both regular release and sustained release forms.

Oral SR-NG, similar to ISDN, was designed specifically for angina prophylaxis rather than for treatment of an acute anginal episode. Unlike ISDN, however, because of its rapid absorption and metabolism, nitroglycerin must be delivered by an SR technology to provide angina prophylaxis (personal communication Rhône-Poulenc). This SR delivery is not currently manufactured as a generic analog. The limited number of studies to date provide poor evidence supporting sustained release efficacy.

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* Preload refers to the pressure/volume status of the heart at the end of the pre-contraction phase of the cardiac cycle.
** Afterload refers to the pressure/volume status of the heart during the contraction phase of the cardiac cycle.
Table 1. Administrative route, dosage and drug costs for oral prophylactic nitrate therapy in British Columbia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual dose range</th>
<th>Cost/month* ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral tablets (Regular release)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISDN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isordil®</td>
<td>10 - 30 mg BID - TID</td>
<td>$ 9.20 - 16.20</td>
</tr>
<tr>
<td>Coronex®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic drugs (Novo-Sorbide®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apo-ISDN®</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oral tablets (Sustained release)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISDN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cedocard®</td>
<td>20 mg BID</td>
<td>$ 28.69</td>
</tr>
<tr>
<td>Coradur®</td>
<td></td>
<td>$ 27.78</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrong-SR®</td>
<td>2.6 - 5.2 mg BID - TID</td>
<td>$ 33.06 - 86.51</td>
</tr>
</tbody>
</table>

*Cost/ month is based on the wholesale acquisition cost as of December 1993 and average provincial dispensing fee of $6.34.

5. DRUG COST AND UTILIZATION PATTERNS

Table 1 shows the dosage and drug costs of the various ISDN and SR-NG tablets prescribed in British Columbia. The four-year trend for B.C. Pharmacare utilization of each drug and delivery form are shown in Figures 1 and 2.

ISDN cost ranges from approximately $0.02 to $0.05 for the highest strength generic regular release tablets, to approximately $0.10 for similar dose regular release brand name tablets. Most commonly, regular release ISDN tablets are recommended in a three times daily schedule. ISDN is also manufactured in a rarely prescribed SR form. These sustained release tablets are usually prescribed twice daily and are more expensive at $0.35/pill. In comparison, SR-NG is made in one strength which costs approximately $0.44 per tablet and is generally used in a twice daily regimen12 (Table 1).
Figure 1. Volume (in millions) of regular and sustained release oral nitrate tablets dispensed in British Columbia, 1990-1993

![Bar chart showing volume of regular and sustained release oral nitrate tablets dispensed in British Columbia from 1990 to 1993.

Figure 2. Total expenditure (in millions) of regular and sustained release oral nitrate tablets in British Columbia, 1990-1993

![Bar chart showing total expenditure of regular and sustained release oral nitrate tablets in British Columbia from 1990 to 1993.

Notes:
In 1993, Coronex® 30 mg ISDN oral tablet not listed.
In Figure 2, the wholesale acquisition cost and dispensing fees for the drugs were included in calculating total expenditure.
Over the past four years, oral nitrate use in B.C. has moved steadily upwards towards long-acting forms (Figure 1). The market share for regular-release ISDN has declined 20%, while SR-NG has risen 50% (Figure 2). SR-ISDN, however, has shown little change representing less than 1% of the market share in 1993. Since the average price per tablet for ISDN and SR-NG has risen only 5% during this period, increased utilization alone accounts for rising Pharmacare costs.

6. APPRAISAL AND ANALYSIS OF RESEARCH REPORTING PRIMARY DATA

6.1 METHODOLOGY

The B.C. Office of Health Technology Assessment has developed standard protocols for the selection and appraisal of primary data relevant to a particular research problem. Data are collected from both university library systems and associated electronic databases as well as the "fugitive literature". Fugitive literature includes material not published in peer-reviewed journals such as reports from evaluative research groups, unpublished research, industry representatives, research and development organizations, technical reports, consensus groups, and technology assessment offices. Studies for review are selected using inclusion criteria which are applied equally to all articles regardless of source. The critical appraisal process is then based on criteria for determining the extent to which the research protocol of the study under review conforms to scientific standards. This ensures that study findings are not accepted unless supported by sound research methodology.

6.1.1 Search strategy

A number of electronic searches were conducted using the following databases: the National Library of Medicine MEDLINE, HEALTH, HSTAR, EMBASE, Current Contents, Drug Information Fulltext, International Pharmaceutical Abstracts, Pharmaceutical News Index, Pharmacoprospects, and Pharmaceutical and Healthcare Industry News Database. The search strategy spanned from 1966 to December 1993 and was limited to studies of human subjects. Key search terms used were "nitroglycerin", "isosorbide dinitrate", "angina pectoris", "drug administration routes", "delayed action preparations", "oral tablets", "effectiveness", and "efficacy".

Information not indexed by electronic databases was sought from the pharmaceutical industry, research and development agencies, and technology assessment organizations. In addition, information was sought directly from the pharmaceutical industry both through meetings with representatives Sept. 29,
1993 and October 13th, 1993 at the University of British Columbia and through a written submission received in the fall of 1993.

6.1.2 Inclusion criteria

The main criterion for inclusion in the critical appraisal process was that the study reported primary data on the efficacy and/or effectiveness of ISDN or SR-NG. Background information regarding the pharmacological properties of alternate nitrate preparations, their therapeutic indications and historical developments of alternate drug delivery technology were also reviewed to provide a general background to clinical and pharmacological issues.

6.2 APPRAISAL PROCESS

Retrieved reports were appraised using methodology based on the work of Chalmers et al and patterned after Schechter and LeBlanc, and Sackett. The standard criteria for assessing studies of therapeutic intervention and those specific to prophylactic anti-anginal therapies are listed in Table 2 and Table 3, respectively. Additional specific criteria, for example, the importance of a cross-over phase in study design, were derived from the scientific literature on nitrates, particularly the work of Silber and Elkayam.

Three categories of studies were identified:

1. Ideal studies were randomized controlled trials comparing efficacy and effectiveness of oral ISDN and SR-NG.

2. Less than ideal but also desirable were studies reporting primary data on ISDN and SR-NG relevant to a reference drug, such as isosorbide mononitrate (ISMN), in a comparable patient population.

3. Minimally acceptable studies were those reporting absolute, that is drug/placebo, efficacy and/or effectiveness studies on ISDN and SR-NG.
1. The population inclusion and exclusion criteria are adequately described
2. The assignment of patients to treatment is randomized
3. Clinically important outcomes, including quality of life, are assessed objectively and blindly
4. The treatment is feasible to use in medical practice in the community
5. There is at least 80% follow-up of subjects
6. Both statistical and clinical significance is considered
7. In the case of a study showing negative results, is power assessed?

Table 2. General appraisal criteria for the therapeutic intervention studies

- A placebo-control phase preceded the study
- The study included a cross-over design
- The study measured the time to onset of angina, documented with greater than 4mm ST segment depression on electrocardiogram, on a graded exercise test
- The incidence and severity of angina pectoris was assessed during normal daily life
- Patient compliance to dosage schedule was measured or at least an attempt made to count the pills used

7. FINDINGS

Twenty-three studies reporting primary data on nitrates were reviewed\textsuperscript{3,10-14,17-33}. However, because the research question focused on assessing relative drug efficacy and effectiveness, few studies were located that provided data suitable for this review. In fact, no studies met the ideal inclusion criteria of comparing a clinical end point with oral ISDN and SR-NG using a single study population. Nor did any studies meet the next to ideal criteria of comparing these two drugs to a reference drug in a comparable patient population.
Seven studies reporting primary data on SR-NG\textsuperscript{10-11} and ISDN\textsuperscript{6,12,17,19,29} were considered minimally acceptable and included in this review. They were appraised according to the criteria listed in Tables 2 and 3. The results of the critical appraisal were examined in relation to five issues which were useful in discriminating between these ISDN and SR-NG. These five issues: tolerance, compliance, side effects, drug interactions and quality of life are discussed below.

7.1 Tolerance

The current debate and the central focus of current research regarding efficacy and effectiveness of oral nitrates for the prophylactic treatment of angina is whether the accepted initial benefit is sustained during ongoing use. Tolerance refers to the generally accepted observation that oral nitrates given in high enough doses for a sufficient length of time frequently produce diminishing and, in some patients, no benefit when compared with placebo. This phenomenon may occur after a few days or up to a one week period\textsuperscript{16,19,29}.

Most evidence supports a nitrate free, or at least a nitrate low, period to sustain nitrate efficacy and effectiveness\textsuperscript{1,16} The most widely accepted protocols involve daytime dosage with nighttime abstinence, termed an "eccentric" dosage schedule. How best to permit sub-therapeutic levels of nitrate to occur while maintaining efficacy and avoiding tolerance development remains controversial.

No studies compared SR-NG and ISDN tolerance development in a single study population. One double-blind randomized study compared SR-NG with isosorbide mononitrate (ISMN), an oral nitrate commonly used in Europe\textsuperscript{11}. It showed an absence of tolerance development to SR-NG using a three times daily dosage schedule in 12 patients over a 4 week period. These results are obviously suspect because of the small numbers involved, infrequent testing, and absent description of patient compliance. Furthermore, the results are difficult to generalize because of coincident use of a long acting beta-blocking agent. No other studies have suggested that the SR-NG is of particular benefit in avoiding tolerance development.

Several longer and more rigorous, double blind, randomized, placebo-controlled, cross-over studies have shown tolerance development with certain ISDN dosages and schedules, and not with others\textsuperscript{1,29,33}. No similarly rigorous studies have examined SR-NG. Therefore, whether or not tolerance develops to this SR-NG at any or all doses and dosage schedules remains essentially unknown.

Thus current evidence is insufficient to distinguish between ISDN and SR-NG in terms of likelihood of tolerance development. However, both drugs seem equally suited for use in the eccentric dosing schedule, defined earlier.
7.2 Patient Compliance

Patient compliance means the degree to which patients take the prescribed amount of medication at the correct time intervals. High patient compliance, or close adherence to drug dosage and schedule, is an often stated goal of drug therapy. Because SR-NG and ISDN differ in their daily dosage schedules, with SR-NG usually recommended twice versus ISDN three times daily, there is a theoretical likelihood that patients will comply more closely with the SR-NG schedule. Closer adherence to dosage schedule is seen as more likely with SR-NG because patients need only remember to take it twice, versus ISDN three times per day. Although reasonable in theory, none of the studies reviewed in this report provided evidence to support this assumption. As well, this assumption may be erroneous because, unlike many asymptomatic conditions such as hypertension, patients with ischemic heart disease have readily recognizable symptoms ranging from mild shortness of breath to angina pectoris and therefore these patients can readily assess their need for medication. Therefore, in the absence of myocardial ischemic pain, patients omitting a nitrate pill may be no worse off physically* and better off therapeutically due to the decreased likelihood of tolerance development.

7.3 Side effects

Side effects of oral nitrates, most commonly headaches and nausea, are almost always transient and considered mild1. No research directly compared side effect profiles of ISDN versus SR-NG in a single study population. Differences in side effect profiles, if they exist, seem unlikely to constitute a significant factor differentiating between these two drugs.

7.4 Drug interactions

None of the studies attempted to examine SR-NG and ISDN in terms of actual or potential drug interactions either with cardiac or non-cardiac drugs.

7.5 Quality of life

Despite a valid and reliable quality of life research tool designed for assessment of anti-anginal therapy6,7, no research was found which compared SR or other long acting with short acting nitrate preparations.

* The current controversy regarding the clinical significance of what is termed "silent", that is painless, myocardial ischemia, is noted. While potentially an important issue to oral nitrates as well as other prophylactic anginal agents, to date the literature provides no evidence considered of relevance to this discussion.
8. DISCUSSION

Beyond the study design characteristics listed in Tables 2 and 3, several additional features are recommended for research relevant to the formulary review process. These are listed in Table 4. The first two characteristics, regarding the need for relative efficacy studies and a gold standard therapeutic agent reflect the gaps in the scientific literature as were illustrated by this report. The third, the need for quality of life assessments, reflects the growing general recognition that patient opinion on effectiveness should play a greater role in determining allocation of scarce health care resources. The final recommendation reflects the need to have primary data on overall patterns of practice, including drug and other therapies, both before and after formulary decisions are made involving an individual drug.

<table>
<thead>
<tr>
<th>Table 4. Recommended drug trial characteristics for the drug utilization review process</th>
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</thead>
<tbody>
<tr>
<td>1. Relative drug efficacy and effectiveness must be measured in a randomly allocated matched population</td>
</tr>
<tr>
<td>2. A standard of therapy, or therapies, should be established within a class of drugs depending on clinical outcomes of interest</td>
</tr>
<tr>
<td>3. Studies should assess quality of life that includes an evaluation of patient opinion regarding drug effectiveness</td>
</tr>
<tr>
<td>4. Studies should examine the overall impact of listing or delisting a drug on the therapeutic practices of a cross section of physicians over time</td>
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</table>

8. CONCLUSIONS

No evidence was found to distinguish between ISDN and SR-NG in terms of efficacy, effectiveness, development of tolerance, patient compliance, significant side effect profile, drug interactions, or influence on quality of life. The most significant difference is the ten fold higher cost of SR-NG, versus generic ISDN, per usual dosage regimen.

Given the increasing utilization of the SR-NG form, and the documented increased costs, this lack of evidence of any significant benefit suggests consideration should be given to the development of guidelines for the appropriate use of the different forms of nitroglycerine provided through the provincial formulary.
The drug utilization and formulary review process places an increased burden on drug manufacturers to demonstrate *relative* as well as *absolute* efficacy of their products. This is particularly important when a drug is considerably more expensive than an established alternative. In future, lack of proof of positive benefit may be sufficient to not list a drug on, or consider withdrawing it from, a formulary payment scheme.
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