Orally Administered Nitrates in Patients with Exertional Angina

Although the efficacy of sublingual nitroglycerin in relieving anginal attacks in patients with ischemic heart disease remains unquestioned, the role of the orally administered, so-called long-acting, nitrates in preventing angina is less certain. Originally, skepticism concerned whether such agents reach the systemic circulation in active forms. Recent studies have demonstrated, however, that within 15 minutes of ingestion, nitrates effect a decrease in left ventricular volume, a fall in systemic arterial pressure, a reflex rise in heart rate, a fall in left ventricular ejection time index, improvement in segmental wall motion, and improvement in exercise capacity. Both the magnitude and duration of the effects appear to be dose-related.

The genesis of the increased exercise capacity following administration of nitrates could involve increased myocardial oxygen supply and/or decreased demand. Both dilatation of coronary arterial stenoses and decreased resistance in coronary collaterals have been observed following nitrate administration and suggest a role for increased supply. Most evidence, however, suggests that more important factors are the decrease in myocardial wall tension and its attendant decrease in oxygen demand brought about by nitrate-induced systemic venous and arterial dilatation. This conclusion is supported by the relief of pacing-induced angina by intravenous nitroglycerin after delivery of the drug directly into the coronary arteries failed to relieve the symptom, and by the relief of pacing-induced angina by phlebotomy alone. The nitrate-induced decrease in left ventricular wall tension and end-diastolic pressure might, of course, not only decrease oxygen demand, but also increase supply by decreasing the resistance to coronary capillary flow, especially in the subendocardial myocardium.

In contrast to orally-administered nitrates, beta-adrenergic blocking agents have received almost universal acceptance as agents effective in preventing exercise-induced angina. Because the drugs decrease myocardial oxygen demand through different mechanisms, beta blockers and sublingually-administered nitrates have been found to have additive salutary effects. In this issue of Chest, Bassan and Weiller-Ravell (see page 233) describe improved exercise capacity following orally administered isosorbide dinitrate in nine of ten patients whose angina was incompletely relieved by propranolol; in eight of the nine the improvement lasted five to eight hours after a dose of the nitrate that lowered systolic blood pressure 20 mm Hg with the patient sitting.

Therefore, that single doses of orally administered nitrates are effective prophylactic antianginal agents, have a dose-dependent relatively long duration of action, and add significantly to the antianginal effects of beta-adrenergic blocking agents seems well established. Many questions, however, are unanswered. Which oral nitrate is most effective? Isosorbide dinitrate is the most thoroughly researched, but other nitrates seem to have similar effects. Which preparation of an effective nitrate is best absorbed? Isosorbide dinitrate tablets and sustained release capsules have been shown to be effective antianginal agents, but patients often complain that the sustained release tablets appear in their stools. Do sublingual, transmucosal, chewable, or transdermal preparations of long-acting nitrates offer any advantages over the oral ones?

The important question of nitrate tolerance continues to be debated. Current evidence suggests that with commonly employed dosing schedules, tolerance to the hemodynamic effects of long-acting nitrates develops within a few days, is never complete, is due to end-organ hyporeactivity and not to accelerated metabolism, and is accompanied by the development of some cross-tolerance to sublingual nitroglycerin. For reasons yet unexplained, improved exercise tolerance persists despite the blunted hemodynamic response at rest. Nitrate dependence, such as occurs in munters, has not been documented with the therapeutic use of nitrates, but would be difficult to distinguish from progression of underlying ischemic heart disease. Similarly, whether in the clinical setting nitrate-induced dilatation of arteries and arterioles supplying normal myocardium ever steals blood from the already maximally dilated arteries supplying ischemic areas is unknown. Such considerations prompt caution in the chronic prescription and/or abrupt withdrawal of long-acting nitrates.

Finally, the role of long-acting nitrates must be redefined in the presence of the calcium ion antagonists. These latter agents have proved highly effective when, as in patients with Prinzmetal’s variant angina, coronary arterial spasm is a dominant feature. In patients with typical exertional angina, however, the beneficial effects of these drugs, like those of nitrates, may result primarily from systemic vasodilatation, and
to what extent calcium antagonists will replace long-
acting nitrates remains to be determined. Unlike the
calcium antagonists, nitrates have no negative in-
otropic effects and may be the preferred drugs in
patients with significant ventricular dysfunction,
whereas nifedipine might be favored in patients with
adequate function and systemic arterial hypertension.

Thus, although nitrates have been used to treat
angina pectoris for at least 115 years and over 1,300
articles have been written about them in the past
decade,19 many questions remain about their mecha-
nisms of action and about the role of oral nitrates in
the long-term treatment of patients with exertional angina.

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Diet-Drug Treatment of
Hyperlipidemia in Coronary
Artery Disease

A Rational and Beneficial Approach

A close relationship between elevated plasma lipid
(cholesterol and triglyceride) and enhanced de-
velopment of coronary artery disease (CAD) has been
well-established by epidemiologic study, animal ex-
perimentation and human premature atherosclerosis.
Clinically, however, the use of diet-drug treatment of
hyperlipidemia for primary or secondary CAD preven-
tion has not gained wide acceptance. Some of the
reasons for the reluctance include: (1) plasma lipid
levels of a significant number of patients with proven
CAD are considered to lie within an arbitrarily set
range of normal, (2) angiographically demonstrable
coronary arterial lesions are not consistently correlated
with hyperlipidemia or hyperlipoproteinemia, (3)
progression and development of new CAD are variable
and unpredictable. The inconsistent association of
the plasma lipid level with CAD is not surprising, in view
of the knowledge that atherosclerosis is a multifactorial
disease. A meaningful correlation between them can
only be consistently demonstrated in certain subsets of
patients, especially those with familial hyper-
cholesterolemia (primary type 2 hyperlipoprotein-
emia), who have a strong predisposition
to CAD.1,2

In human subjects, plasma lipid (cholesterol) levels
are delicately regulated by well-balanced compensa-
tory mechanisms of excretion, feedback regulation and
tissue storage. Disturbance in one or more homoesta-
tic mechanisms is manifested in one or the other types
of CAD-prone hyperlipoproteinemia or hyper-
lipidemia. Thus, the ongoing debate about the virtues
of imposing "prudent diet" on the population in general1,4
not only misses the point, but confuses the
patient and physician. Clearly, there is little need for
dietary or other forms of intervention in subjects who
can maintain normal lipid metabolism, but a specific
diet-drug treatment should be prescribed for a well-
defined type of disturbance in lipid metabolism.

Patients with familial hypercholesterolemia (pri-
mary type 2 hyperlipoproteinemia) exemplify the need
for and benefit from aggressive intervention with diet-
drug treatment. In this abnormality, a defect in the
cellular low density lipoprotein (LDL) receptor sites
has been defined, and an effective combination of low
cholesterol-saturated fat diet with colestipol and nico-
tinic acid or probucol treatment has been developed6,9
to facilitate cholesterol elimination and to reduce
cholesterol (LDL) biosynthesis. Several groups of
investigators have reported encouraging data to sug-
gest that progression of CAD can be retarded and early