総 説 (Review)

Current Concepts of Nitrate Therapy

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The organic nitrates have been employed for more than a century in the management of patients with coronary artery disease and myocardial ischemia. Lauder Brunton[1] described the beneficial effects of amyl nitrite in patients with angina pectoris in 1867 and William Murrell[2] documented the efficacy of nitroglycerin (GTN) in patients with angina pectoris in 1879. He reported that patients with angina pectoris improved when a 1% solution of GTN was administered prophylactically and that patients obtained relief when they took this medication during an episode of angina pectoris. This was the first report of the efficacy of GTN as an agent for angina prophylaxis and also as a therapeutic intervention to treat episodes of ischemia.

Mechanism of Action of the Nitrates

The organic nitrates are prodrugs and require a metabolic change to induce their therapeutic effects. This biodegradation occurs in vascular smooth muscle cells where the organic nitrate, in association with reduced sulfhydryl groups are denitrated to produce nitric oxide (NO). NO stimulates the enzyme guanylate cyclase which leads to the production of cyclic guanosine monophosphate (cGMP). cGMP induces vasodilatation by reducing the availability of intravascular calcium to the contractile proteins in vascular smooth muscle[3] (Figure 1).

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It is now recognized that NO is identical to the endothelium derived relaxing factor (EDRF) and it is possible that exogenous nitrates may be able to replace EDRF in situations where there is endothelial dysfunction such atherosclerosis, hypertension, hypercholesterolemia and congestive heart failure.

Within endothelial cells, the enzyme NO synthase leads to the production of EDRF from L-arginine. EDRF produced by endothelium

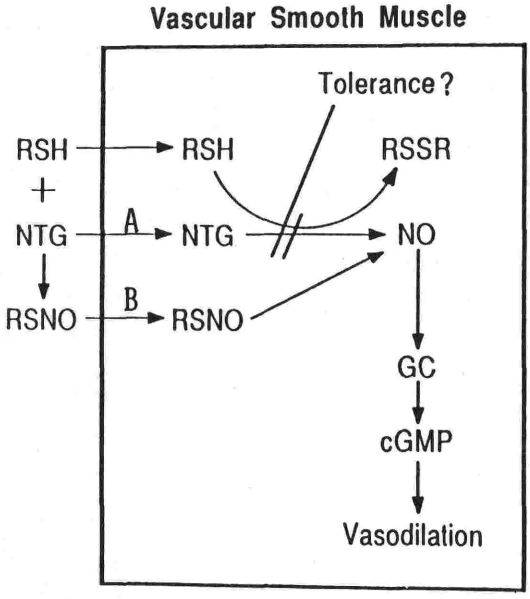

Figure 1. The organic nitrates are metabolized within vascular smooth muscle cells to produce nitric oxide (NO). Nitric oxide stimulates guanylate cyclase with the production of cyclic GMP (cGMP) which induces vasodilatation.

causes relaxation of underlying vascular smooth muscle cells. EDRF production is increased in situations of increased blood flow and EDRF modulates the vascular response to many vasoconstrictor agents including serotonin, norepinepherine, thrombin and ADP. Another important function of EDRF is its effect on platelet function. It has been shown that EDRF reduces platelet adhesiveness and modifies platelet aggregation. This effect may be important as it is recognized that such processes may be involved in atherogenesis. EDRF also has anti-coagulant effects with the local production of plasminogen activator substances. EDRF reduces endothelial adhesion for macrophages and also inhibits growth factors, alterations that may affect the process of atherogenesis. The major question is whether exogenous nitrates which lead to the production of NO can replace the beneficial effects of EDRF in clinical situations characterized by impaired endothelial function.

Hemodynamic Effects of the Nitrates

The nitrates are vasodilators and exert their effects on capacitance veins and conductive arteries. The venous dilatation reduces left ventricular filling pressures and thus lowers preload. This change reduces myocardial oxygen requirements and the diminished filling pressures may augment subendocardial coronary blood flow. The nitrates have effect on arterial or resistance vessels in the doses used clinically but by dilating conductive arteries lower arterial impedence and thus reduce left ventricular afterload. The diminished afterload reduces myocardial oxygen requirements. The nitrates as well have been shown to dilate coronary collateral vessels and augment blood flow to ischemic areas. It is important to recognize the effects of the organic nitrates on the arterial bed quite different from agents such as dipyridimole or the dihydropyridine class of cacium entry blockers. These agents have potent arteriolar effects which may have a deleterious effect on the distribution of coronary blood flow. They augment coronary blood flow but this may produce the phenomenon of coronary steal by redistribution of blood from ischemic to non-ischemic areas of the myocardium (Figure 2).

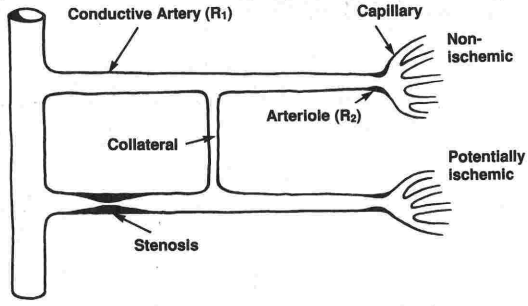

Figure 2. The organic nitrates dilate the epicardial conductive arteries and collateral vessels. They have no effect on other resistance vessels.

Tolerance to the Organic Nitrates

It is now recogized that nitrate tolerance is a common problem in clinical practise. This should not have been surprising as we have known for years from animal studies that increasing doses of nitrates could be given with decreasing effects on blood pressure and heart rate[4,5]. Likewise, workers in the munitions industry commonly had severe headaches and other side effects from nitrate exposure but there symptoms cleared within a short period of time[6]. Workers also found that after a weekend away from work, they would have recurrence of there side effects when they return to work on Monday morning. This observation indicated that tolerance not only occurred rapidly but was rapidly reversed. These workers learned to apply the nitrates to their skin or clothing over the weekend to maintain their state of tolerance while away from work.

Tolerance was documented in clinical practise

in 1888 when Stuart reported that the initial beneficial effect of organic nitrates in treating hypertension was rapidly lost during continued therapy[7]. The importance of nitrate tolerance in patients with angina pectoris was initially documented by investigators in Germany and Canada. Studies by Rudolph et al showed that the anti-ischemic effects of isosorbide dinitrate (ISDN) were rapidly attenuated and they also demonstrated that hemodynamic tolerance occurred rapidly as assessed by changes in pulmonary capillary wedge pressure at rest and during exercise. Such hemodynamic tolerance has been repeatedly shown in the systemic circulation[7,8,9]. In 1982 a study with multiple doses of ISDN was reported[10]. A group of patients with stable angina pectoris and reproducible exercise tests were studies. In this placebo controlled trial, patients were tested acutely with dose of 15, 30, 60 and 120 mg of oral ISDN. During acute therapy, each dose of ISDN produced a substantial decline in standing systolic blood pressure which become less marked during the eight hour observation period but the hypotensive response persisted in comparison to placebo. The patients subsequently entered the sustained phase of the study where they received one week of therapy with each ISDN dose and placebo with the medications administered four times daily i. e. with meals and at bedtime. In comparison to the hypotensive effects seen during acute ISDN administaration the response during sustained four times daily therapy was reduced with each dose by approximately one half and the hypotensive effect persisted for only four hours rather than eight hours as acute therapy. During the initial administration, there was a dose response relationship with a greater effect being seen with the larger doses but with sustained therapy in such

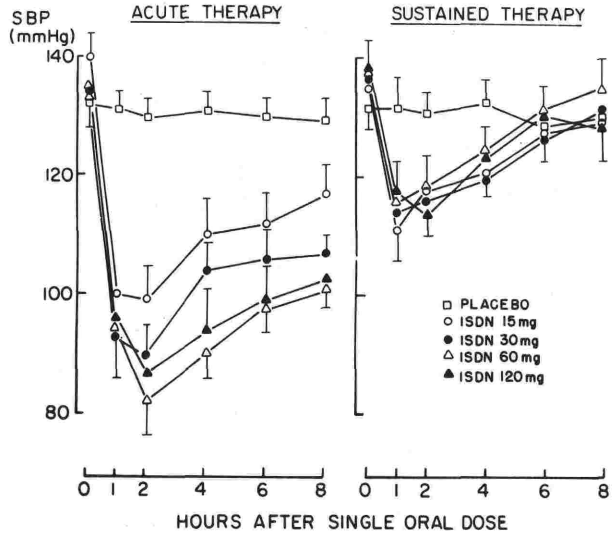

Figure 3. Oral isosorbide dinitrate (ISDN) when given acutely in a single dose, produce a significant decline in blood pressure with each dose and the effects persist for up to eight hours. During sustained four times daily therapy, the extent and duration of the decline tn blood pressure reduced and there was no longer any evidence of a dose response relationship.

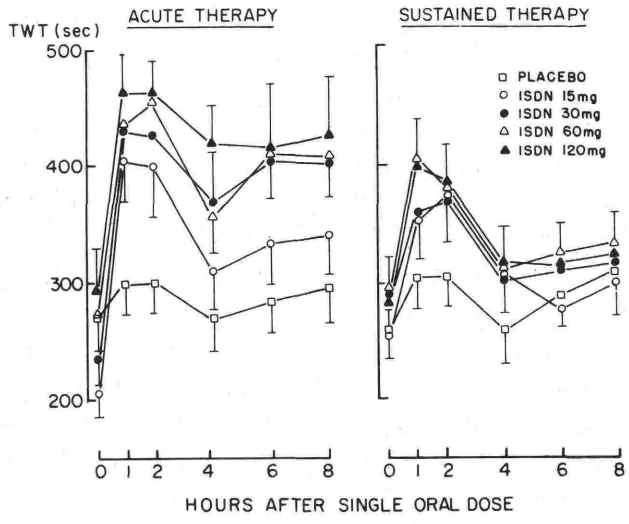

Figure 4. Isosorbide dinitrate (ISDN) when given orally in single doses, produces a substantial increase in treadmill walking time (TWT) to the development of angina (P_1) and the time to moderate angina (P_2). The effects persists for six to eight hours. When ISDN was given four times daily in sustained therapy, the effect was diminished in maginitude and persisted for only two hours after dosing. This tolerance cannot be overcome by employing the larger doses.

dose response effect was documented (Figure 3).

More importantly, the results of treadmill exercise testing showed dramatic attenuation of the anti-anginal effects (Figure 4). During acute administration, each dose of ISDN produced an improvement in exercise duration over that seen with placebo for a period of eight hours. However, after only one week of sustained four times daily therapy, improvement persisted for only two hours after dosing and this was significantly less than seen during acute therapy. The dose responce effect on exercise performance seen during acute therapy was not apparent during sustained therapy. This study documented that the administration of larger doses of ISDN in this dosing regimen had no effect on preventing nitrate tolerance. These observations which clearly documented tolerance to the hemodynamic and anti-anginal effects of ISDN during continuous therapy were contrary to previous studies with oral ISDN[11,12]. The explanation for these disparate findings is unclear but may be related to the time interval between the administration of the evening dose and the exercise test the following morning. It is recognized that tolerance is rapidly reversed and in some of these investigations the morning exercise test was done 12 hours or more following the last dose administration, a period that could have reversed tolerance.

Transdermal Nitroglycerin

Transdermal GTN onitment has been employed for many years in the treatment of angina pectoris and congestive heart failure. There have been several published reports documenting the beneficial effects of

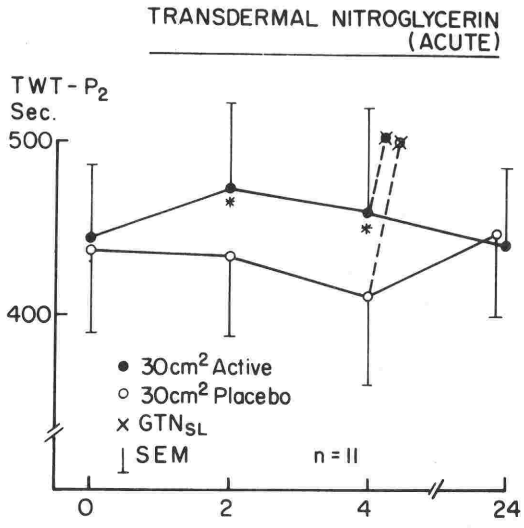

Figure 5. Transdermal nitroglycerin application in a dose of 30 cm^2 (0.6 mg/hour) improved exercise performance two and four hours after dosing but there was no effect at 24 hours. This documented the early development of tolerance.

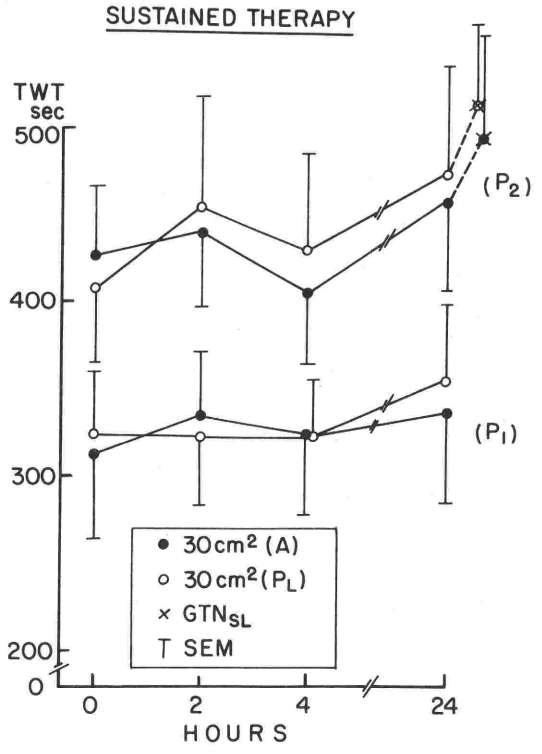

Figure 6. When the transdermal nitroglycerin is applied once daily and left in place for 24 hours, complete tolerance occurs if there is no significant difference between active and placebo medication.

nitroglycerin ointment on exercise tolerance in patients with angina. These reports have documented improvement in exercise tolerance for up to seven hours after application[13], but there is only one study in which the effect of GTN ointment was assessed during sustained therapy. This study by Reicheck and co-workers looked at exercise tolerance following three times daily application of GTN ointment[14]. They documented the improvement in exercise time but unfortunately testing was done three hours after ointment reapplication and there are no date relating to their efficacy on exercise tolerance later in the dosing period.

Transdermal GTN patches were introduced in Europe and North America more than a decade ago were initially considered to provide continuous anti-ischemic and anti-anginal effects when put in place each day and left for 24 hours. The initial studies in patients with angina pectoris documented clinical improvement as documented by exercise testing at the end of the 24 hour period of patch application[15-17]. Subsequently, well controlled studies however provided quite a different picture indicating that while the patches were effective during acute therapy, tolerance developed repidly[18,19]. In addition, during continuous once a day application, studies appeared showing that there was complete tolerance with this mode of administration[18] (Figure 5, 6). These conflicting results lead to the transdermal GTN co-operative study in the United States in which patients with chronic stable angina were studied[20]. Patients were required to have reproducible exercise testing and also to show improvement in exercise tolerance when exercise was carried out after the subl-

ingual administration of 0.4 mg of GTN. After meeting these entry criteria, patients were placebo patches for two weeks and then where randomized to receive either placebo patches once daily for a period of eight weeks or to active therapy. All patients receiving active therapy initially received a patch delivering 0.6 mg per hour. Exercise testing was carried out before, 4 and 24 hours after patch application. After a week of such therapy, one cohort remained on that dosage but over the next five weeks, groups of patients were uptitrated so that the end of the titration period there were patients receiving placebo patches and GTN patches delivering 0.6, 1.2, 1.8, 2.4, 3.0, 3.6 and 4.2 mg per hour. Exercise testing was carried out at weekly intervals before 4 and 24 hours after patch application. Following the initial patch application, those patients receiving active therapy (0.6 mg per houer) showed an improvement in treadmill walking time four hours after patch application but by 24 hours the effects were no greater than placebo (Figure 7). During the titration period and at the end of the study period, exercise tolerance before, 4 and 24 hours after patch application was similar in the placebo group to each of the GTN treated group (Figure 8). This well controlled study which completed the assessment in 562 patients confirmed the fact that continuius GTN patch application was associated with complete tolerance in the majority of patients and was not clinically useful. This study also documented that tolerance could not be prevented by using very large doses of transdermal GTN administered continuously.

Mechanisms of Nitrate Tolerance

There is incomplete understanding of the factors responsible for nitrate tolerance. The most widely accepted hypothesis is that during nitrate exposure, reduced sulfhydryl groups that are required for the denitration of nitrate to nitric oxide are depleted. This depletion dur-

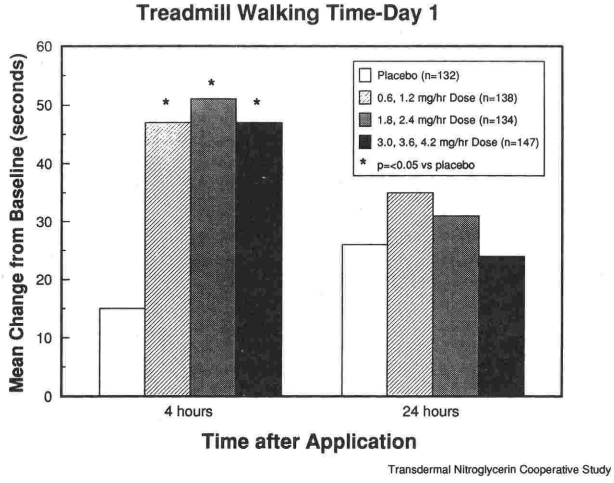

Figure 7. The change in treadmill walking time from the baseline four and 24 hours after initial therapy with transdermal nitroglycerin delivering 0.6 mg per hour. Treadmill walking time was improved four hours after initial administration but by 24 hours patients receiving active and placebo medication had a similar change in exercise tolerance indicating the presence of tolerance.

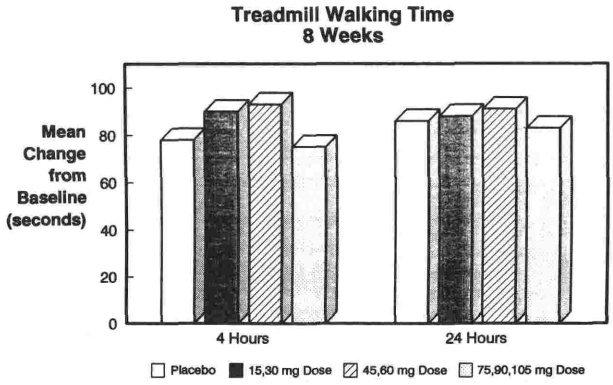

Figure 8. At the end an eight week period of once daily application of transdermal nitroglycerin, the changes in treadmill walking time from baseline four and 24 hours after the morning application was similar in the placebo group and those receiving a low, medium and high dose continuous nitroglycerin administration. This documented that the problem of tolerance could not be overcome during continuous therapy by using large doses of transdermal nitroglucerin.

ing continued exposure to the organic nitrates leads to diminished NO production and ultimately reduced production of cGMP[21]. The other postulated mechanism for nitrate tolerance is that neurohormonal activation occurs during nitrate therapy. This leads to increased plasma concentrations of catecholamines, arginine vasopressin and activation of the renin angiotesin system[22]. These changes could lead to augmentation of vasoconstrictor forces and changes in fluid balance. Short term studies have demonstrated sodium retention and water with a resultant decrease in hematocrit[22] but longer term studies have shown that the initial sodium and water retention is reversed although the fall in hematocrit persists[23, 24]. This suggests that nitrates may lead to a fluid shift from the extravascular to intravascular compartments by modifying the Starling forces.

Prevention or Reversal of Nitrate Tolerance

The sulfhydryl group depletion hypothesis has attracted most attention as the mechanism for nitrate tolerance. Several studies have assessed the effect of the administration of sulfhydryl groups with agents such as N-acetylcysteine (NAC) and methionine. NAC has been shown to potentiate the effects of nitrate induced vasodilation[25] and during tolerance induced by continued nitrate administration, studies have shown that NAC may partially reverse tolerance[26, 27]. There is some debate whether this effect truly reflects reversal of nitrate tolerance or merely a change in the nitrate dose-response relationship following NAC administration. The role of sulfhydryl group depletion has been challenged by the lack of effect of NAC on exercise tolerance in patients made tolerant with four times daily therapy with ISDN[28]. It has been suggested that the

effect of NAC on nitrate tolerance is due to modification of an extracellular pathway with production of a nitrosothiol which enters vascular smooth muscle cells and releases NO (Figure 1). Because such extracellular conversion with ISDN is slow it is suggested that this explains the lack of effect of intravenous NAC during tolerance induced by ISDN. This hypothesis supported by the negative studies in heart failure with methionine[29]. Methionine can only provide sulfhydryl groups intracellularly and the absence of beneficial effects following methionine administration during nitrate tolerance provides evidence that intracellular sulfhydrly group depletion may not be important in the pathogenesis of nitrate tolerance.

The evidence that neurohormonal activation occurs during nitrate therapy has lead to studies attempting to prevent the development of tolerance. The use of converting enzyme inhibitors in angina pectoris has been shown to prevent tolerance in some patients during continuous GTN patch application[30]. Using forearm plethysmography, Katz and co-workers have shown that both captoril and enalapril prevent tolerance in normal volunteers receiving continuous transdermal GTN patches[31]. However, in normal subjects receiving continuous GTN patch application, tolerance to the blood pressure and heart rate effects of transdermal GTN occurred as rapidly during therapy with the converting enzyme inhibitor benazapril as it did during placebo therapy[23]. This study suggests that activation of the renin angiotensin system during nitrate therapy may not be of importance in the pathogenesis of nitrate tolerance.

The evidence of increased intravascular volume has lead to studies looking at the effect of diuretics on the development of nitrate tolerance. In a preliminary study in patients with stable angina pectoris, Sussex and co-workers gave patients ISDN 30 mg four times daily, a regime known to induce nitrate tolerance[32]. In a cross over study, patients received concomitant therapy with hydrochlorothiazide or placebo. The efficacy of ISDN on exercise performance during ISDN therapy was lost during four times daily therapy when patients were given placebo. However, when hydrochlorothiazide and oral ISDN were co-administered, tolerance did not develop. The beneficial effects of concomitant diuretic and nitrate therapy in angina has however, not been confirmed by subsequent studies. Studies from our laboratory suggest that the addition of a diuretic has no effect on the development of tolerance during nitrate therapy[24]. In normal volunteers, hemodynamic tolerance occurs within 24 hours of the institution of continuous transdermal GTN patch applecation. In a placebo controlled trial, we found that the concomitant administration of hydrochlorothiazide in identical doses employed by Sussex et al had no effect on the time course or degree of tolerance during continuous transdermal GTN patch application. Thus, at the present time, there is no clear evidence that modification of the neurohormonal responses induced by nitrate administration has any significant impact on the development of tolerance.

Intermittent Nitrate Therapy

With incomplete understanding of the mechanisms responsible for tolerance and the conflicting evidence for the efficacy of the administration of sulfhydryl groups, converting enzyme inhibitors and diuretics in reversing or preventing tolerance how dose one approach the problem of the prevention of nitrate tolerance? Observations in munitions workers suggested that tolerance develops rapidly nitrate exposure and is quickly reversed during nitrate withdrawal. When patients are given oral ISDN, tolerance develops rapidly and is reversed within several hours of nitrate withdrawal. Studies with patients with chronic stable angina pectoris, have shown that

tolerance, as assessed by treadmill exercise, develops during four times daily ISDN therapy, a strategy designed to provide therapeutic effects for prolonged periods during each 24 hours[10]. By omitting the evening dose, tolerance is reversed and the effect of the morning dose during sustained three times daily therapy is similar to that seen with initial dosing[28]. While this strategy of intermittent ISDN therapy has been shown to prevent tolerance as assessed by exercise testing carried out after the morning dose, there is concern regarding the effectiveness of subsequent ISDN doses given later in the day. Indeen, Bassan[33], in a small number of selected patients who were tested during intermittent therapy with oral ISDN documented that treadmill walking time was prolonged for only an hour after the second and third dose during such intermittent therapy. These observation are contrary to recent studies with standard formulation isosorbide-5-mononitrate given eccentrically at 7 and 14 hours where significant benefits, as assessed by treadmill exercise, were documented at 7 hours after the 14 hour dose during sustained therapy[34].

The effectiveness of intermittent therapy with transdermal GTN patches, have been confirmed by the intermittent trabsdermal GTN study[35]. When the transdermal patches were applied 12 hours each day for a period of four weeks with a 12 hour washout period, beneficial effects and exercise performance were seen between eight and 12 hours after patch application. It is important to note however that exercise performance decreased progressively during the patch on period indicating that partial tolerance developed over the first 12 hours of patch application.

Rebound Effects

As tolerance develops during nitrate therapy there is concern that during nitrate withdrawal rebound phenomena may occur. This was first noted in munitions workers where acute ischemic events including unstable angina pectoris, myocardial infarction and sudden death occurred during periods away from the work environment[36]. This typically occurred during the latter part of the day on Sunday or early on Monday morning before returning to work. Autopsy studies or coronary angiography usually showed no significant coronary artery disease and it has been postulated that these clinical events were related to coronary vasospasm occuring as the nitrate induced vasodilatation diminished during the period of nitrate withdrawal. This is in keeping with recent studies documenting neurohormonal activation during nitrate administration which could lead to coronary vasoconstriction.

The other, more recent evidence suggesting rebound was seen during the intermittent transdermal GTN study[35]. In this study, nine patients on active therapy has an increase in their rest angina during the pariod of patch removal. None of the patients on placebo therapy reported any change in their pattern of angina. Similar observations were reported by Ferrantini et al in patients with stable angina pectoris where pain during the patch off period was increased[36].

Another suggestion of rebound was in the so called "zero hour effect". In the intermittent transdermal GTN study, patients receiving active therapy and placebo showed a progressive improvement in the exercise duration in the morning test before patch reapplication[35]. The increase over the baseline execise test was however, greater in those patients who received placebo throughout this four week trial than those who received active therapy. It has been suggested that this difference in response may be secondary to rebound phenomena that occur in patients receiving active therapy. Thus, if vasoconstrictor influences were activated during the period of active patch application, temporal dissociation between nitrate withdrawal and the

decline of vasconstrictor influences could be associated with reduction in coronary flow and thus diminished exercise performance. Clearly further investigations are required to ascertain whether or not significant untoward effects do occur during intermittent nitrate therapy.

It is apparent that despite the long time use of organic nitrates in clinical practice, we have more to learn about this group of agents. The knowledge that NO, the active metabolic of the organic nitrates is identical to EDRF is of great potential importance. It remains to be documented whether exogenous nitrates can replace the many actives of EDRF in conditioning of endothelial dysfunction. Thus, it is possible that the nitrates may be more than vasodilators and could play a role in the prevention or modifying progression of atherosclerosis decrease.

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