Review Article

An update on nitrate tolerance: can it be avoided?

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Introduction

Organic nitrates have been recognized by physicians as potent vasodilators and effective therapy for angina pectoris for over 100 years.^{1,2} Despite the advent of beta-blockers and calcium channel antagonists in the 1960s the organic nitrates remain important antianginal agents and are well-established as the drugs of choice in acute angina. Recently interest in nitrate therapy has increased as a result of the widespread use of intravenous nitrates in coronary care, and in the management of acute heart failure and because of this, their inclusion in the ISIS-4 study.

The excellent response to acute nitrate administration led to a search for a method of giving nitrate therapy prophylactically. Unfortunately initial attempts were disappointing because, in many instances, chronic dosing with either oral or transcutaneous preparations was associated with the development of tolerance and results in significant attenuation of the antianginal effect. This loss of effect threatened to prevent the successful long-term use of an apparently effective and safe form of therapy for patients with angina. This review will therefore focus on the evidence for tolerance, the possible mechanisms which cause it and the therapeutic attempts that have been made to circumvent it.

Historical perspective

Even in the earliest reports of amyl nitrate use in angina pectoris there was evidence that progressively larger doses were required to achieve a satisfactory therapeutic response.¹ The first report of haemodynamic tolerance was made by Stewart who noted that persistent use of nitroglycerin (NG) led to attenuation of the side effects of headache and flushing.³ This early clinical observation led to the first major review of the subject in 1905 in which Stewart advocated the use of the 'nitrate free' interval as a means of avoiding tolerance.⁴

The widespread use of nitrates in the munition factories became a recognized source of industrial exposure amongst those who manufactured nitroglycerin. Elbright⁵ reported that, although the headaches associated with the production of nitroglycerin rapidly subsided during continued exposure, this 'immunity' was quickly lost outside the working environment. Swartz⁶ went on to show that the reappearance of symptoms ('Monday head') could be prevented by applying nitrates to the skin or clothing over the weekend. Animal studies have similarly confirmed the development of tolerance in all species tested, both *in vivo* and in isolated vascular preparations. Furthermore, treatment with one nitrate compound can induce a state of 'cross-tolerance' to other nitrates.⁷

The pharmacodynamic effects of organic nitrates occur in all areas of the cardiovascular system. It is therefore necessary, when discussing nitrate tolerance, to specify which haemodynamic response is being assessed. For example, higher doses of nitrates are required to dilate the arterial circulation than the venous capacitance vessels.⁸ The former effect is responsible for the hypotensive action and the headache associated with therapy, while the latter effect is mainly responsible for venous pooling and preload reduction that underlies much of the beneficial action in angina pectoris. It is now well-established that there is rapid tolerance to the hypotensive action of nitrates making these drugs ineffective antihypertensive agents.⁹ However, because functional studies of the venous circulation are technically difficult it is not easy to make direct assessments of tolerance to the venous actions of nitrates. Only indirect measurements such as pulmonary capillary wedge pressures and exercise time to angina are available. In addition, since the antianginal effect is not only a reflection of the venodilatation but may also depend to some extent on arterial and coronary vasodilatation,¹⁰ it is not surprising that no clear consensus has emerged from the studies addressing the issue of nitrate tolerance in stable angina pectoris.

Modern evidence

Oral nitrates

From the 1960s onwards oral nitrate preparations became widely available for the prophylaxis of angina pectoris. A number of early reports suggested that the aims of 24 hour antianginal cover (as assessed by exercise tolerance testing) had been realized by 3–4 times daily dosing regimens with isosorbide dinitrate (ISDN),^{11,12} isosorbide-5-mononitrate (IS-5-MN)^{13,14} and oral NG.^{15,16} However, these encouraging studies were followed by increasingly widespread reports of partial or complete tolerance to the anti-ischaemic effects of both oral ISDN and IS-5-MN, its principal metabolite in the body.

These studies employed non-sustained release preparations of ISDN at a dose of 15–120 mg 6 hourly and assessed antianginal efficacy using treadmill walking time (TWT) to angina. In general, the first dose of ISDN reduced blood pressure and prolonged TWT but sustained, regular treatment led to partial or complete attenuation of these responses.^{17–19} However, the development of tolerance was less marked if the last two doses of the day were omitted.¹⁸ In another study, ISDN 100 mg given continuously as a transdermal ointment²⁰ prolonged TWT for 8 hours after the first application but there were no effects demonstrable at 24 hours. After a week of sustained therapy no benefit could be seen at any time during the 24 hour dosing period. This loss of response occurred after sustained treatment despite substantially higher blood levels of ISDN and its metabolite IS-5-MN. This suggested that the tolerance phenomenon was truly a pharmacodynamic rather than pharmacokinetic effect. Furthermore, this 'continuous' method of administration produced complete tolerance compared with only partial attenuation resulting from four times daily oral ingestion of the same drug.¹⁷ This may reflect the difference between even and uneven plasma nitrate levels and may partly explain some of the inconsistent results found with respect to tolerance development in the literature (see below). The studies of the antianginal effects of IS-5-MN have led to similarly confusing results. While sustained antianginal efficacy has been shown with 20 mg 8 hourly^{13,14,21} others have shown tolerance development at 50 mg 8 hourly.^{22,23}

That the findings from the many studies of oral nitrate therapy are so divergent is interesting and requires explanation. Since both the onset of tolerance following nitrate exposure and the loss of tolerance following withdrawal are very rapid, even very short periods of low nitrate levels may allow some recovery of nitrate responsiveness.²⁴ Thus explanations include irregularity of dosing, inter-

mittent non-compliance and variability in the timing of the exercise tests in relation to nitrate doses.^{9,17}

Transdermal nitrates

The development of the transdermal NG patch has made a great impact on the treatment of stable angina pectoris. This method of nitrate delivery has proved convenient for patients and is known to rapidly produce steady-state plasma levels lasting throughout the 24 hour dosing period.²⁵ However, this method of continuous administration has initiated a reappraisal of the role of nitrates in angina and reopened the tolerance debate. Many investigations of continuous patch therapy have demonstrated that rapid development of tolerance occurs following an initial beneficial response.^{26–31} The improvement in exercise tolerance following patch application is seemingly lost within 12 hours of the first patch application.³² However, tolerance to the antianginal effects of the NG patch is by no means a universal finding with many apparently well-conducted studies coming to the opposite conclusion.^{33–36}

To address the problem of tolerance to the NG patch the Food and Drugs Administration multicentre trial was set up in 1985 after the granting of conditional status to these preparations in the USA.³⁷ The study was randomized, double blind and placebo-controlled in design and involved a total of 562 patients with baseline TWT of 3–7 minutes (Bruce protocol). After initial patch applications of 15 mg/day, significant benefits were noted at 4 hours but the effect had been lost at 24 hours indicating the rapid onset of tolerance. Although TWT improved by a mean of 90 seconds at the end of the active therapy phase, this did not differ significantly from the control group who benefited from a non-specific training effect from the regular exercise tests. The trial design allowed for cohorts of patients to have weekly increments in dosage but even up to 150 mg/day no return of antianginal efficacy could be achieved. This clear demonstration of rapid and complete tolerance was significant in that it involved much greater numbers of patients than previous reports.

There is inconsistency between the results of studies of the efficacy of the NG patch that cannot be explained by uneven plasma levels. A number of other factors may have been important (Table I). Marked variations exist in the number of patients, the duration of the study, the daily dose of NG and the method of exercise testing.^{38,39} However, the factor likely to have been of greatest importance was the use of concomitant antianginal therapy. Some studies recruited patients with stable angina who completed the study period using their usual antianginal medication as well as the nitrate patch,

Table I The factors involved in producing inconsistent results in studies addressing the question of nitrate tolerance

Patient numbers
Concomitant antianginal therapy
Beta-blockers
Calcium antagonists
Inconsistent patient selection
Age
Severity of angina
Nitrate responsiveness
Nitrate dosage
Timing of exercise tests (in relation to doses)
Training effect of regular exercise tests
Placebo antianginal effects
Irregular tablet taking or non-compliance with oral medication producing a nitrate-free interval

others withdrew current medication before entry and some used patients previously untreated. The concurrent use of beta-blockers in particular has been accused of masking the potential benefits of the patch. Although some of these studies have suggested sustained benefits from the patch,^{40,41} a demonstration of long-term efficacy seems to be most likely when nitrates are used as monotherapy.^{33–35,42,43} Conversely, studies satisfying the criterion of including subjects on nitrate therapy alone can be criticized for bias towards long-term nitrate responders who might be less readily susceptible to tolerance. The ideal trial seems to be one using nitrates alone in previously untreated patients, although the results may not be applicable to the general population of angina sufferers.

It is also possible that genuine and significant subjective improvements in the frequency of symptoms and lifestyle may be made in the absence of objective benefits as assessed in the artificial surroundings of the laboratory. The TWT may be a relatively crude indicator of overall antianginal efficacy and the impact of the non-specific training effect may have been underestimated. In several studies conducted over a period of weeks, the placebo group have made significant improvements in exercise capacity.^{37,44,45} Therefore studies that have relied on these parameters as markers of sustained antianginal efficacy must be interpreted with caution.⁴¹

The exercise test performance may also be subject to a number of non-drug related influences such as ambient temperature, relationship to food, emotional status and a diurnal rhythm that may be related to autonomic nervous activity. Episodes of silent and symptomatic myocardial ischaemia are more frequent in the early hours of the day and this may explain why, during continuous patch application, the '24 hour test' has been the one least likely

to show a significant improvement. This has major implications as the vast majority of studies of single patch application have indicated the loss of efficacy at 24 hours. If there was no diurnal variation to account for then tolerance at 24 hours should persist. However, it has been consistently shown that even after weeks of therapy and consequently near constant NG levels there may be improvements in daytime exercise capacity despite the apparent presence of tolerance prior to the morning patch application. This seems to imply a background influence which at its greatest (24 hours) suppresses any nitrate effect but may allow the benefits of drug treatment at other times (4 hours post application).

Conclusions

Although there has been marked variability in patient selection, concurrent medication and experimental protocol, there seems little doubt that the regular use of organic nitrates of various kinds is associated to a greater or lesser extent with the development of tolerance. Tolerance seems to occur to the antianginal, haemodynamic and side effects of nitrates although the former remains the most contentious issue. Whether the level of nitrate exposure is a predisposing factor or whether there are certain groups protected from the onset of tolerance remains to be determined. It is clear that sustained and even nitrate exposure is most likely to produce tolerance.⁴⁶ For this reason the long-term benefits of nitrate patches have been a matter of considerable debate, although there are undoubtedly many patients who have benefited from this treatment. When it has been observed, tolerance has usually been apparent within 12–24 hours of the onset of therapy. Such a rapid decline in efficacy is obviously a serious disadvantage in the clinical setting the ultimate aim of therapy is 24 hour anginal prophylaxis. Just as the onset of tolerance is rapid so too is the return to full nitrate responsiveness following the termination of treatment.²⁴

Mechanisms of nitrate tolerance

Although the basis of nitrate tolerance remains incompletely understood, a number of recent studies have helped to clarify the situation. They have suggested that tolerance results from either the activation of counteractive cardiovascular reflexes or altered responsiveness of vascular smooth muscle following prolonged exposure (Table II). The possibility that tolerance resulted from a change in pharmacokinetics or altered drug handling has been considered but seems most unlikely. There is no evidence for changes in

Table II Potential mechanisms underlying the development of tolerance to the haemodynamic and antianginal effects of the organic nitrates

Neurohumoral activation
Plasma volume expansion
Plasma renin activity
Catecholamines
Vasopressin
Sulphydryl depletion theory
Decreased nitrate metabolism

absorption, distribution or elimination that might reduce nitrate concentrations during chronic dosing. In fact, tolerance to either oral or transdermal ISDN seems to occur despite higher plasma levels of ISDN or its metabolite IS-5-MN.^{17,20}

Neurohumoral activation

Chronic nitrate exposure causes a variety of hormonal and haemodynamic changes in response to its vasodilating action. These include an elevation of plasma catecholamines, vasopressin and activation of the renin–angiotensin system.^{47–50} These responses are likely to help to restore the peripheral vascular resistance by increasing vasomotor tone in the arteriolar resistance vessels and probably explain the tolerance to the hypotensive action of nitrates. The impact of neurohumoral changes on the effects of nitrates on venous capacitance vessels and by extension their role in angina and heart failure is less well established. However, following intravenous infusions of nitroglycerin a reduction in sodium excretion, an increase in weight and a fall in haematocrit have been documented.^{50–52} These changes imply a degree of haemodilution and plasma volume expansion which might offset any initial gains made as a result of nitrate-induced preload reduction on the heart. In this way the initial beneficial effects of venous pooling would be overcome.

Sulphydryl depletion

A major advance in the understanding of nitrate tolerance was made following *in vitro* studies by Needleman and colleagues that suggested tolerance arose by altered pharmacodynamic effects at the vessel wall.⁵³ In particular, it was proposed that cytosolic sulphydryl groups, which seemed to be necessary for nitrate activity, could be critically depleted in vascular smooth muscle during chronic therapy leaving the vessels refractory to further treatment. Further experiments established that nitroglycerin could activate the soluble enzyme guanylate cyclase in cell preparations to form cyclic guanosine-3, 5-monophosphate (cGMP) and that

the presence of cysteine, a sulphydryl group donor, was essential for this to occur.^{54,55} The production of cyclic GMP then appeared to induce smooth muscle relaxation by reducing cytosolic free calcium whether by activating a Ca^{2+} -extrusion ATPase or causing sequestration of calcium in the sarcoplasmic reticulum.⁵⁶ However, it was the steps between the entry of exogenous nitrates to the smooth muscle cell and the activation of guanylate cyclase that seemed to hold the key to the tolerant state (Figure 1). These steps are apparently dependent on the availability of sulphydryl donors.^{57,58}

These ideas were elaborated by Ignarro *et al.*⁵⁹ who showed that NG was metabolized in the smooth muscle cell by reacting with sulphydryl groups to form unstable intermediates called S-nitrosothiols. These compounds could then in turn interact with the haem moiety of guanylate cyclase to liberate nitric oxide.⁶⁰ Nitric oxide has been known for several years to activate guanylate cyclase and to be the likely metabolite ultimately responsible for nitrate-induced vasodilatation.^{55,61} However, considerable interest has been focused on its role since the publication of evidence by Palmer and colleagues⁶² suggesting that nitric oxide was either identical to or a mediator of endothelium-derived relaxing factor (EDRF). EDRF was first recognized by Furchgott and Zawadzki in 1980 as an endogenously formed unstable radical capable of smooth muscle relaxation and inhibition of platelet aggregation secondary to stimulation of soluble guanylate cyclase.⁶³ Thus exogenously administered nitrates have been considered as pharmacological substitutes for EDRF, the ‘endogenous nitrate’ produced by the vascular endothelium.⁶⁴

Is there evidence for a role of sulphydryl depletion in nitrate tolerance? *In vitro* support for this

Figure 1 A putative model for the steps leading to nitrate-induced vasodilatation. While the traditional organic nitrates require sulphydryl groups for an intermediate reaction this is not the case for sodium nitroprusside or 3-morpholino-sydnnonimine (SIN-1), the metabolite of the nitrate vasodilator molsidomine.

concept comes from studies on isolated vascular preparations showing that arteries rendered tolerance to nitrates will regain responsiveness on addition of sulphhydryl donors such as cysteine or N-acetylcysteine.⁶⁵⁻⁶⁷ Tolerance to nitrates seems to involve a reduced capability to stimulate guanylate cyclase rather than an effect on the enzyme itself which remains responsive to protoporphyrin IX,⁶⁸ a direct acting stimulant.

Studies of nitrate-tolerant patients offered sulphhydryl group repletion have so far given conflicting results. Some authors have reported potentiation of nitrate-induced vasodilatation following treatment with either N-acetyl cysteine infusion⁶⁹⁻⁷² or oral methionine.⁷³ However, patients who had developed tolerance to four times daily ISDN showed no immediate recovery following N-acetyl cysteine infusion⁷⁴ and oral methionine seemed unable to reverse the tolerance induced by intravenous nitroglycerin in heart failure.⁷⁵ One study aimed specifically at tolerance to antianginal effects of the NG patch found equal tolerance to 10 mg/24 hours at 4 days whether a placebo or N-acetyl cysteine was given simultaneously.⁷⁶

Two nitrate drugs, sodium nitroprusside and molsidomine, are considered to lead directly to nitric oxide production without the need for sulphhydryl group donors at an intermediate stage.⁷⁷ Therefore the fact that tolerance developed in a study of 10 patients with stable angina whether given ISDN or molsidomine seems to suggest that sulphhydryl depletion alone may not be the only factor and that other mechanisms such as neuro-humoral activation may also play an important role.⁷⁸ Finally, current evidence suggests that during chronic nitrate exposure and tolerance plasma nitrate levels actually increase.¹⁷ This suggests that the metabolic breakdown is impaired in parallel with the attenuation in pharmacological effect and invites speculation that the two processes are linked.⁷⁹ It seems likely that much of the metabolism of organic nitrates does occur in the peripheral vessels themselves rather than in the liver as was originally thought. Of course a reduction in nitrate metabolism during tolerance would be in keeping with the sulphhydryl group depletion theory but other metabolic blocks cannot be excluded. It

has also been suggested that inactive nitrate metabolites may prevent normal uptake and metabolism of the active drug.⁷⁹

The prevention of nitrate tolerance

Although the cause or causes of the tolerance phenomenon have not yet been fully established, attention has progressively focused on possible methods of circumventing the problem (Table III).

The nitrate-free interval

Whatever the contribution of individual mechanisms might be, it is clear that in most situations tolerance seems to be only a temporary phenomenon which spontaneously disappears when nitrates are withdrawn.²⁴ Most investigators have therefore tried to maintain the efficacy of regularly administered nitrates by including a 'washout' or 'nitrate-low' period within the dosing regimen. In this way a number of studies have shown modification of antianginal tolerance to ISDN,^{18,19,80} IS-5-MN^{81,82} and transdermal NG patches.^{29,44,83-86}

Eccentric dosing

Rudolph was the first to suggest and subsequently demonstrate that the attenuation of haemodynamic responsiveness could be avoided by providing a nitrate-free period.¹⁹ ISDN given in regular 6 hourly doses rapidly resulted in loss of antianginal efficacy. However, when ISDN was taken at 8 am and 1 pm ('eccentric' dosing) giving low night time nitrate levels, post-dose exercise endurance remained improved after a week. A 15 day comparison of intermittent therapy with buccal GTN and regular oral ISDN showed TWT at 1, 3 and 5 hours post-dose remained prolonged compared to placebo on day 15 with the intermittent buccal but not the oral therapy.⁸⁷ After their clear demonstration of tolerance in patients assigned four times daily ISDN,¹⁷ Parker's group re-examined the problem and found that antianginal efficacy could be preserved if the last one or two daily doses were omitted.¹⁸ However, even with this type of eccentric dosing regimen it seems that the second and third doses are each less effective than the first.⁸⁸

Sustained-release preparations

Newer sustained release oral nitrate preparations (Cedogard Retard, Isoket Retard, Imdur, MCR-50, Monit SR, Elantan LA 50) have allowed the aims of interval therapy to be achieved with a convenient once daily dosage. Studies with both sustained-release ISDN and IS-5-MN confirm that

Table III Possible mechanisms for avoiding tolerance

'Nitrate-free' or 'washout' period
Eccentric dosing of oral medication
Sustained-release oral preparations
Patch removal
Phasic-release patches
Sulphydryl repletion
ACE inhibitors - captopril
Diuretics

the antianginal response to once daily treatment is maintained, although inclusion of a second evening dose led rapidly to tolerance.^{82,89} Although a twice daily regimen (8 am, 8 pm) seems to be unsuccessful, an alternative eccentric arrangement of sustained-release doses (8 am, 3 pm) succeeded in avoiding tolerance.⁹⁰ When sustained-release IS-5-MN 60 mg once daily was compared with ISDN 30 mg four times daily improved TWTs were seen at 4, 8 and 12 hours⁹¹ on IS-5-MN once daily.

Intermittent patch therapy

With many questions having been raised about the long-term efficacy of transdermal patches, a number of authors have assessed the possible benefits of intermittent patch application. The Transderm Nitro Trial Study Group performed a large study of 206 patients with angina assigned to placebo, 5–10 mg/day or 15–20 mg/day of NG by transdermal patch.⁴⁴ Patients under simultaneous treatment with beta-adrenoreceptor antagonists were not excluded from the study. TWT was assessed at 0, 4, 8 and 12 hours on days 0, 1, 15 and 29. Patches were applied at 8 am and removed at 8 pm on each day throughout the duration of the study. Subjects taking the higher (but not the lower) dose continued to have statistically significant improvements in TWT at both 4 and 8 hours for the duration of the study suggesting that at this dosage tolerance had been avoided. A surprising finding was that patients on placebo could exercise longer at time 0 on day 29 implying that a 'rebound' deterioration in exercise endurance had developed during the nitrate washout period. In this context it is noteworthy that nine patients had a marked increase in anginal episodes during the patch-off period.

In a much smaller double-blind crossover study, Ferranti *et al.*⁸⁶ compared the use of continuous or intermittent (12 hour nitrate-free interval) nitroglycerin patches as monotherapy (20 mg/day) in 10 male patients with stable angina. At the end of each active treatment period lasting 15 days, exercise tests were performed at 4 and 12 hours post-dosing. Intermittent patch treatment significantly increased the ischaemic threshold at the 4 and 12 hour test compared to the continuous patch regime. Night time NG withdrawal was associated with 11 anginal episodes in six of the subjects who had previously been free from nocturnal attacks. These occurred at an average of 2 hours after patch removal, a time when nitrate levels are known to decline sharply.²⁵ This finding again supports the concept of a 'rebound' ischaemic effect following nitrate withdrawal. Other studies have failed to demonstrate such a dramatic withdrawal effect,^{29,84} although the simultaneous administration of other antianginal medication may have masked it.

The intermittent use of NG patches failed to overcome tolerance in a few studies, particularly when the nitrate-free interval was less than 12 hours.^{92,93} A comparison of the activation of neurohumoral mechanisms during 24 or 12 hour patch applications suggested that intermittent therapy was not associated with any sodium or water retention and only partial neurohumoral activation in contrast to the significant increases during continuous therapy.⁵⁰ This result seems to offer a logical rationale for the use of intermittent patch therapy and suggests that at least in this situation neurohumoral activation could be avoided by intermittent therapy.

It is now generally accepted that a period of nitrate withdrawal or at least low level exposure is necessary within the daily regimen if tolerance is to be avoided. However, the withdrawal of nitrates may not be without hazard. In particular, the sharp falls in NG levels following patch removal may be associated with a rebound effect ischaemia.^{44,84,86,93,94} Therefore, despite the promising benefits of intermittent dosing regimes in overcoming tolerance, there may be a price to be paid with the potential exacerbation of ischaemia. The rapid withdrawal of an exogenous vasodilator seems to allow the endogenous vasoconstrictors to become temporarily dominant.⁹⁵ This effect may be masked by the concomitant administration of other antianginal agents. Both the occurrence of rebound and its suppression by beta-blockade offer further support for the concept that there is some neurohumoral response to exogenous nitrates.

We might therefore ask if there is an ideal pharmacokinetic profile that might give therapeutic cover during the day, allow a nitrate-low interval at night but provide a sufficiently gentle decline in levels to overcome the problem of rebound. With this aim the pharmaceutical industry has provided some promising sustained release oral preparations and the newer phasic release patches that release the majority of their dose in the first 12 hours. Further assessment of these preparations will be required, although the initial results are encouraging.^{96,97} A fundamental problem that remains with interval therapy is whether it is possible to cover the prewaking hours adequately when silent myocardial ischaemia is particularly prevalent.

Sulphydryl repletion

With attention focused on the possible role of sulphydryl depletion, a number of studies have attempted to use sulphydryl group donors to reverse tolerance but the results have been conflicting.^{71,74,98}

While some studies have successfully re-established haemodynamic responsiveness to nitrates

using N-acetyl cysteine,^{69,71,98,99} the reversal of antianginal tolerance has in others not been possible.^{74,76} Although these repletion studies have advanced our understanding of tolerance, there must be doubt expressed as to whether these techniques are a practical option in the clinical setting. The evidence suggests at best that only intravenous or high dose oral therapy is effective and the latter may be associated with limiting side effects.⁷¹

Captopril and angiotension converting enzyme inhibitors

Since reflex neurohumoral activation may be an important factor in the development of tolerance some investigators have examined the possibility of intervening with angiotensin-converting enzyme inhibitors. The role of captopril deserves special mention, since its effects may not only involve suppression of the renin-angiotension system. Captopril also contains a sulphhydryl grouping which, as previously discussed, may potentiate the pharmacodynamic response to nitrates in the tolerant state. A number of reports have confirmed that captopril can to some extent prevent tolerance and potentiate the actions of NG in angina.^{34,100} Subjects rendered tolerant to the antianginal effects of ISDN over 3 weeks once again showed improved exercise capacity when captopril was given 1 hour prior to exercise testing.¹⁰¹ Both captopril and to a lesser extent enalapril reduced haemodynamic tolerance to nitroglycerin patches as assessed by forearm plethysmography.¹⁰² Thus it seems that, although both drugs were effective, captopril's sulphhydryl group may confer some advantage over enalapril. In another attempt to separate the two possible effects of captopril, rat aortic rings were prevented from developing tolerance *in vitro* by both captopril and N-acetyl-cysteine but not enalaprilat.¹⁰³ In an isolated perfused heart model (where the effects of systemic vasoactive substances such as angiotensin II are presumably not active) captopril and cysteine but not non-sulphhydryl containing converting enzyme inhibitors could act synergistically with ISDN.¹⁰⁴ It has also been shown that captopril has the potential to react with nitric oxide to form S-nitrosocaptopril, a molecule which acti-

vates guanylate cyclase to cause smooth muscle relaxation even in the tolerant state.¹⁰⁵ The potential production of a vasodilating product is interesting in view of the current interest in the role of these drugs in influencing local vasomotor control systems.

Diuretics

Since regular nitrate therapy causes plasma volume expansion which may be a factor in producing tolerance,^{51,52} the use of diuretics to suppress this compensation has also been examined. When given the ISDN, hydrochlorothiazide preserved the initial anti-ischaemic effects offering further support to the fluid retention hypothesis.¹⁰⁶

Conclusions

There seems little doubt that tolerance to regular nitrate therapy is a real and clinically significant phenomenon. Although our understanding of its causes is not yet complete, there is good evidence for both altered sensitivity of the blood vessel to nitrates as well as the activation of a number of neurohumoral reflexes that may suppress their pharmacological effect. Since tolerance is likely to be multifactorial in aetiology, any single pharmacological intervention is unlikely to prevent it. Whatever its cause tolerance is rapid in onset but also short-lived.²⁴ For this reason intermittent therapy seems to be an attractive solution with good experimental support. However, it is not yet clear as to whether a nitrate-low or nitrate-free interval is more desirable. This question takes on greater importance given the evidence supporting the occurrence of a rebound phenomenon which may be a major hazard in clinical practice. Current research must address the dilemma of providing a safe washout period without jeopardizing the long-term benefits of chronic nitrate therapy.

In the meantime, the available evidence suggests that organic nitrates are still useful agents for antianginal prophylaxis. Whether oral or transcutaneous preparations are prescribed physicians should incorporate a nitrate-low period during each 24 hours for maximum benefit.

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