# Action of glyceryl trinitrate (GTN) in angina pectoris

**Lalith Mendis**[1]

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## Action of glyceryl trinitrate (GTN) in angina pectoris

It is now known that organic nitrates release Nitric oxide in the cells when they interact with the SH (Sulphydryl) group in the vascular smooth muscle. Nitric oxide stimulates soluble guanylate cyclase, resulting in an increase in cyclic guanosine monophosphate. This inhibits calcium mediated contraction.[1]

(It must be recalled that the adrenergic receptor agonism acts by an increase in cyclic adenosine mono phosphate enhancing calcium mediated contraction).

Endothelium Derived Relaxing Factor (EDRF) is released as a response to shear stress felt by the endothelium when an increased flow down-stream demands a vasodilation. EDRF is now known to be Nitric Oxide or a labile Nitroso compound that liberates Nitric Oxide. Even when angiography does not show overt atherosclerosis, many people over 30 years show a decreased EDRF release. Even those vessel segments that have a decreased EDRF release dilate well with GTN.[2]

Hence GTN will have a protective effect on vessel segments which are overtly non-atherosclerotic yet have a decreased EDRF response. However, when these vessel segments develop overt atherosclerosis they cannot respond to GTN.

### Tolerance

Tolerance is likely to develop on continuous Nitrate exposure. Hence it is useful to have a Nitrate-free period during the 24 hours when patients are on long term Nitrates.[3]

Rebound angina that can occur with Nitrate withdrawal in a patient on long-term GTN, can be prevented by using (Isosorbide Mononitrate) (ISMN) which has a smoother withdrawal action.[4] However, even with long term GTN such rebound problems are occasional. It is preferable to prescribe beta blockers to guard against the possibility of rebound.

Biotransformation of GTN to Nitric Oxide requires intracellular sulphydryl groups.[5] The former explanation for the development of tolerance was the depletion of intracellular — SH groups. Credence was lent to this belief by apparent potentiation of GTN by N-acetyl cystein. However, it is now known that such potentiation was caused by an extracellular interaction between GTN and N-Ac cys releasing an active compound.[6]

Tolerance to GTN is the result of impaired biotransformation to nitric oxide, because nitroprusside and EDRF continue to act on smooth muscle cells that develop tolerance to GTN.[7] However the exact mechanism of tolerance is not known.

### Antiplatelet effect

EDRF inhibits platelet aggregation.[1] Though GTN too inhibits platelet aggregation in vitro, this effect may not be adequately felt in vivo because GTN depletes SH groups in platelets. Since GTN acts via cGMP and prostacyclin acts by cAMP, the antiplatelet activity of GTN (if any) will be synergistic to prostacyclin.[8]

### Physiological actions

Nitrate have the following physiological actions.

1. Decreases systolic myocardial tension by arteriolar vasodilatation (after-load decreased) Hence decreases ejection time. This action is slightly offset by the increase in heart rate and velocity of myocardial contraction. However the beneficial effect outweighs the latter. Net result is a decrease in myocardial oxygen consumption. Beta blockers act the other way about. Hence the effects are additive.

2. Nitrates produce more venodilatation than arteriolar vasodilatation. Hence the end diastolic volume (preload) and venous return are decreased. The subendomyocardial region which is at risk from ischaemia is better perfused when the diastolic ventricular volume is lower.

3. Nitrates can dilate epicardial arterioles that enter at right angles to the myocardium. Thus a higher oxygen level in the subepicardial region produces a better oxygen gradient across the myocardium even up to the at-risk

1 *Lecturer, Dept of Pharmacology North Colombo Medical College, Ragama.*

subendocardial myofibrils.

4. The Nitrates dilate the precapillary arteriolar collaterals. Thus taking the increased blood supply of healthy arterioles to the capillary bed of diseased arterioles via precapillary arteriolar collaterals.[9]

5. Laurence asserts that (Clinical Pharmacology — pg 507. 6th Edn) organic nitrates dilate the main coronary arteries.

6. If there is spasm of a coronary artery, nitrates will lyse the spasm. (Relax the tone of coronary arteries). Certainly GTN relaxes "dynamic-stenoses".

7. Another action may be postulated tentatively based on the foregoing discussion. EDRF depleted vessel segments respond poorly to shear stress even before atherosclerosis can be demonstrated angiographically. Continuous Nitrate administration at this stage (with an interval of course to prevent tolerance) may help such segments by causing dilatation, thus preventing intimal damage from shear-stress.

8. Antiplatelet action of GTN, if any, will obviously contribute to its anti-anginal properties.

Fear of GTN causing harmful redistribution of blood away from ischaemic areas were probably unfounded. Though Laurence's Clinical Pharmacology makes much of this, it is routine now to give GTN (oral or iv) in myocardial infarction, especially with persistent pain or acute LVF.

**References**


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