Transdermal Nitroglycerin (Glyceryl Trinitrate)  
A Review of its Pharmacology and Therapeutic Use  

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Summary

Nitroglycerin (glyceryl trinitrate) has been used for many years via the sublingual route for treating acute anginal attacks. In recent years transdermal delivery of nitroglycerin has gained popularity for prophylaxis against angina. However, nitrate tolerance appears to be a therapeutic problem with all long-acting nitrates regardless of delivery mechanism, and it occurs in most patients with stable angina treated with continuous 24-hour application of nitroglycerin patches. Since continuous 24-hour plasma concentrations of nitroglycerin do not appear to be desirable, alternative approaches to therapy are needed. A simple method to minimise tolerance with transdermal nitroglycerin patches is to remove the patch at bedtime and reapply a new patch in the morning. Such intermittent therapy allows a patch-free period during the night, when most patients experience few angina attacks, but optimises nitrate sensitivity during the daytime. However, the place of intermittent nitroglycerin patch therapy in the treatment of stable angina needs clarification with further study, particularly comparisons with other long-acting forms of nitrates. There are insufficient data to recommend the use of transdermal nitroglycerin patches in the treatment of patients with unstable angina or congestive heart failure.

In conclusion, transdermal nitroglycerin patches offer a convenient and cosmetically acceptable dosage form which has potential use in stable angina if administered as an intermittent regimen providing a patch-free period each night.

Pharmacological Profile

The numerous formulations of nitroglycerin patches, while using different technologies in their manufacture, essentially achieve the same pharmacological end-point at equivalent doses, i.e. the constant release of the drug across the skin into systemic circulation for 24 hours which achieves constant steady-state plasma concentrations of nitroglycerin.

The primary anti-ischaemic mechanism of action of nitroglycerin is believed to be relaxation of vascular smooth muscle. The biochemical events leading to vascular relaxation remain unknown, but are thought to include effects on cyclic guanosine monophosphate production to induce contractile protein relaxation, and the possibility that nitrates may be physiological substitutes for endothelium-derived relaxing factor (EDRF). Nonetheless, consequent vasodilatation leads to a reduction in preload and cardiac oxygen demand. A number of other mechanisms have been hypothesised, with recent evidence strongly suggesting an additional direct anti-ischaemic effect produced by improved coronary blood flow. In patients with congestive heart failure the higher doses that are generally used may produce a reduction in afterload from arteriolar dilatation, as well as the more important reduction in preload.

Systemic bioavailability of nitroglycerin is about 75 to 90% following patch administration. The drug is detected in plasma 30 to 60 minutes after application, steady-state plasma concentrations persist from 2 to 24 hours, and no drug is measurable in plasma within 1 hour of patch removal. Mean steady-state plasma concentrations are about 0.2 \( \mu g/L \) after a patch dose of 0.4 mg/h and are directly proportional to the dose administered. There may, however, be wide intra- and interindividual variation; up to 10-fold differences have been noted. This is probably related to the large volume of distribution (3 L/kg); plasma nitrate probably accounts for no more than 1% of the total body nitrate pool. The site of patch application does not affect absorption, but exercise or sauna may increase the rate of absorption from nitroglycerin patches. A phasic release nitroglycerin