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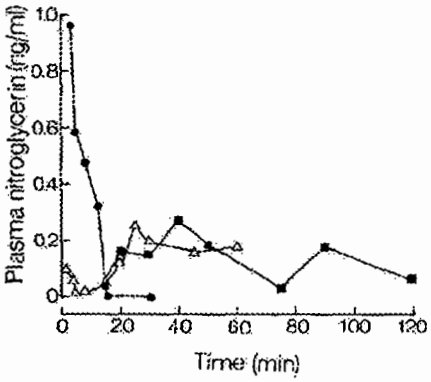
PLASMA NITROGLYCERIN LEVELS AFTER SUBLINGUAL, ORAL AND TOPICAL ADMINISTRATION

Nitroglycerin is administered clinically through any one of three routes: sublingual, oral or topical. While the therapeutic efficacy of the sublingual tablets is well established, the clinical utilities of nitroglycerin oral tablets and ointments are less well defined. The effectiveness of oral nitroglycerin is currently under serious debate. Metabolic studies (Needleman, Lang & Johnson, 1972) showed extensive first-pass metabolism of the drug in the liver, suggesting complete destruction of orally administered nitroglycerin. However, a recent clinical study (Winsor & Berger, 1975) has convincingly demonstrated significant clinical improvement of angina pectoris in patients given oral controlled release tablets. Nitroglycerin ointment appeared to elicit significant hemodynamic changes. After topical application of 15 mg of nitroglycerin, a significant decrease in left ventricular end-diastolic pressure started within 15 minutes and lasted until at least 60 minutes (Parker, Augustine, Burton, West & Armstrong, 1976). None of the studies, however, reported the plasma concentrations of nitroglycerin after drug administration.

Our group has recently improved a gas chromotographic assay (Rosseel & Bogaert, 1973), extending quantitation of nitroglycerin in human plasma to levels as low as 0.1 ng/ml. The method involved stabilization of the drug in plasma with silver nitrate, followed by multiple extraction using specially purified hexane. After addition of isosorbide dinitrate as the internal standard, the hexane extract was concentrated and injected into a glass column packed with 3% SP-2401 on 100/120 supelcoport 01-1991 (Supelco, Inc., Bellefonte, Pa., U.S.A.). The column was maintained at 140° C and quantitation was effected *via* a Nickel-63 electron capture detector. This improved technique allowed us to compare, apparently for the first time, the plasma nitroglycerin levels obtained from clinical doses of the drug through the three routes of administration. In a pilot study of a healthy volunteer, we have followed plasma nitroglycerin levels after administration of (i) a 0.3 mg sublingual tablet, (ii) a 2.5 mg and a 6.5 mg sustained-release oral capsule, and (iii) 1″ of a 2% ointment (corresponding to 16 mg of nitroglycerin). The pulse rate and sphygmomanometric blood pressure of the sitting subject were concomitantly recorded.

Figure 1 shows the plasma nitroglycerin levels obtained after administration of the various dosage forms. As expected, high drug levels were almost instantaneously achieved after the sublingual tablet, reaching about 1 ng/ml at the first measured data point (3 min). Thereafter, the plasma levels declined rapidly and no measurable nitroglycerin levels were detected after 16 min. In contrast, levels above 0.1 ng/ml of the drug were not observed until 20 min after application of the



Figures 1 Plasma nitroglycerin concentrations after administration of a 0.3 mg sublingual tablet (•), a 6.5 mg oral capsule (▪) and application of an ointment containing 16 mg of nitroglycerin (▵).

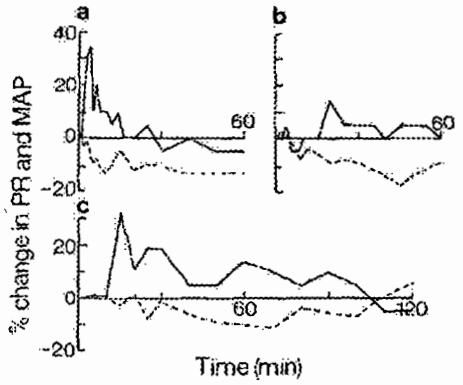


Figure 2 Percent change in pulse rate (PR, ——) and mean arterial pressure (MAP, ...) after nitroglycerin administration (a, 0.3 mg sublingual tablet; b, 16 mg topical application; c, 6.5 mg oral capsule).

ointment and administration of the 6.5 mg capsule. The peak levels achieved from these dosage forms were in the vicinity of 0.2-0.3 ng/ml, which were maintained from about 20-60 min after drug administration. A detectable level of nitroglycerin (about 0.1 ng/ml) was still observed at 120 min after administration of the 6.5 mg capsule. Blood sampling for nitroglycerin was not carried out beyond 60 min after ointment application.

The percent changes in pulse rate and mean arterial pressure after nitroglycerin administration are shown in Figure 2. Changes in these haemodynamic parameters appeared to mirror those of plasma nitroglycerin levels. Both the ointment and the 6.5 mg oral capsules elicited somewhat more sustained haemodynamic effects than the sublingual tablet. The 2.5 mg oral capsule did not give any significant plasma levels of nitroglycerin, nor did it elicit any significant changes in pulse rate and mean arterial pressure.

In summary, we have been able to demonstrate measurable plasma levels of nitroglycerin after oral and topical administration in one subject. Quantitation of plasma levels may be a valuable aid in determining the relative effectiveness of nitroglycerin administered through different routes.

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