L. Pharmacokinetics of Vasodilating Agents

I. Nitroglycerin

Studies on the metabolism of nitroglycerin in various animal species have shown distinct differences making it problematic to extrapolate from experimental animal data to humans. Needleman et al. (1972) found complete inactivation of nitrates following oral administration in rats as a result of the first-pass effect in the liver.

The metabolism of glyceryl trinitrate consists of a stepwise enzymatic cleavage of nitro groups into glyceryl dinitrates, mononitrates and ultimately, into glycerin. The degradation products apparently possess only minor vasodilating activity. Degradation occurs primarily in the liver by the enzyme nitrate ester reductase. Glyceryl trinitrate can also be hydrolyzed in the blood either spontaneously or enzymatically into di- and mononitrates.

Pharmacokinetic data on glyceryl trinitrate (nitroglycerin) are of recent origin. Within the last few years, the technique of gas chromatography has been developed to assay blood levels of nitroglycerin (Crosseel and Bogaert 1973).

1. Sublingual Nitroglycerin

Armstrong et al. (1979) studied the blood level curves after sublingual administration of 0.6 mg of nitroglycerin in healthy volunteers. Nitroglycerin could be detected in the blood as early as 30 seconds after administration and peak levels are achieved after one minute. After 2 minutes, the concentration of nitroglycerin was 2.3 ± 0.36 ng/ml. One-half of the peak level was attained after 7.5 minutes. Twenty to thirty minutes after the initial dose, blood levels were low (Fig. 110). These changes are accompanied by a parallel drop in arterial systolic blood pressure and an increase in heart rate. Pitt et al. (1982) reported similar findings.

2. Intravenous Administration of Nitroglycerin

There is a good correlation between the injected dose and the plasma levels achieved. An increase in the infusion rate from 15 to 100 μg/minute (=0.9 – 6.0 mg/hr) resulted in blood levels of between 1.2 and 11.1 ng/ml (Armstrong et al. 1980a, b). With very high doses up to 440 μg/min (26.5 mg/hr), serum levels increased up to 70 to 480 ng/ml. The serum half-life is approximately 2 to 3 minutes. The extremely large volume of distribution of 100 to 350 liters demonstrates nitroglycerin’s high affinity for tissue proteins. Only 1 to 2 percent of the administered dose is detectable in the plasma.
Intravenous Administration of Nitroglycerin

Clearance is 30 to 80 liters per minute. Various explanations for this high clearance are reported by Jähnchen (1982). A dosage error may result from nitroglycerin adsorption to plastic materials of the infusion kit (see paragraph c). Furthermore, spontaneous hydrolysis in the blood must be kept in mind. And finally, the strong binding of nitroglycerin to erythrocytes may give the appearance of a rapid “clearance” rate.

a) Accumulation in the Vascular Wall

It is also known that nitroglycerin accumulates to a large degree in the vascular wall at the injection site. This level of accumulation decreases with increasing distance from the site of injection (Fung et al. 1981). In general, venous vessels show a higher affinity for nitroglycerin than arterial vessels. This is in line with the specific activity of nitroglycerin in the venous limb of the vascular system. The determination of plasma concentrations in arterial blood always results in higher values than in venous blood samples.

b) Dose-Response Curve in the Venous and Arterial Beds

Imhoff et al. (1980) investigated the relationship between serum concentration and hemodynamic effects. Arterial dilation increased with rising serum concentrations from 0.1 ng/ml to 2.3 ng/ml. On the other hand, maximal venous dilation had already occurred at low plasma concentrations of 0.1 to 0.6 ng/ml. This effect could