

levels may be increased for a longer time in the former group than in the latter, since we observed that the anticataleptic action of L-dopa was shorter in rats pre-treated with Ro 4-4602, and the action decreased during the 2 h observation period.

Spiroperidol-induced catalepsy seems to be particularly resistant to the antagonistic action of L-dopa and is not antagonized by apomorphine (unpublished results).

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*Institute of Pharmacology,
Polish Academy of Sciences,
Kraków - 52, Ojcowska Street, Poland.*

J. MAJ
Z. KAPTURKIEWICZ
J. SARNEK

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Plasma levels in man of nitroglycerin after buccal administration

A major problem in the therapy of angina pectoris is how to prolong the undisputed beneficial effects of buccal nitroglycerin. For evaluation of retard preparations and so-called long acting nitrates, knowledge of the plasma levels of different preparations would be an advantage. Results in man have been reported for pentaerythritol tetranitrate (Davidson, Miller & DiCarlo, 1971); for nitroglycerin valid data are only available in animals (Lang, Johnson & Needleman, 1972); the few papers on plasma levels in man are unacceptable due to the lack of specificity and sensitivity of the method used (Berry & Roach, 1968; Ritschel & Clotten, 1970).

We recently reported a sensitive method for specific determination of nitroglycerin, using gas chromatography with electron capture detection (Rosseel & Bogaert, 1972). The procedure can be used for determination of nitroglycerin in plasma. After centrifugation of the blood at 4°, the plasma (*ca* 5 ml) is removed and extracted three times with 5 ml of ethyl acetate of high purity (Carlo Erba, pro pesticidi). The extracts are passed through Norite filters and evaporated to near dryness under nitrogen, at room temperature. The residue from the three extractions is dissolved in 0.5 ml ethyl acetate, filtered again through a Norite filter, evaporated and dissolved in 10 μ l of benzene. 1 to 2 μ l of this solution is injected in the gas chromatograph.

Before the extraction procedure, isosorbide dinitrate is added to the plasma as internal standard. The ratio of the peak area of nitroglycerin to peak area of isosorbide dinitrate shows a linear relation to the ratio of the quantities of the two injected substances, as ascertained by control experiments. With this method, concentrations of nitroglycerin as low as 0.5 ng/ml of plasma can be specifically measured.

The method was used for measurement of plasma levels in man after buccal administration of nitroglycerin; this route was chosen because of its importance as a reference treatment of angina. Doses of nitroglycerin from 600 to 2500 μ g, dissolved in 0.12 ml of ethanol were introduced in the mouth of young healthy volunteers; they were asked to circulate, without swallowing, their saliva in the mouth for 3½ min, at that moment they expelled their saliva, rinsed their mouth, and venous blood samples were taken at different times thereafter.

Fig. 1 shows the results in 5 volunteers: plasma levels are clearly higher for the

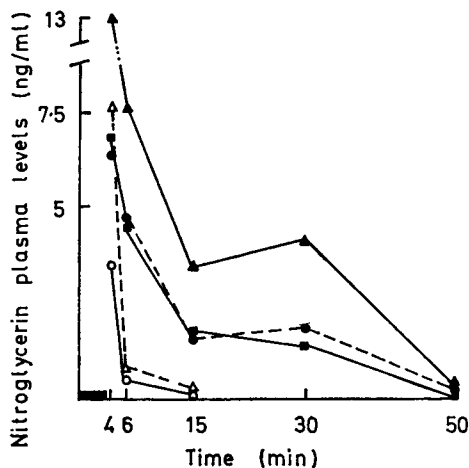


FIG. 1. Plasma levels of nitroglycerin, in ng/ml, at different times after buccal administration of nitroglycerin, 800 μg in 2 volunteers (open symbols), 1200 μg in 3 volunteers (closed symbols). Black bar shows the 3½ min buccal contact time, after which the contents of the mouth is expelled.

higher doses than for the lower, and fall rapidly to zero (i.e. non-detectable, lower than 0.5 ng/ml). One of the subjects whose levels are shown in the figure for 1200 μg , was, on other occasions, given 600 and 2500 μg ; a good dose relation for the plasma levels was seen. In one subject, plasma levels were followed every 30 s during the buccal contact time of the drug and immediately thereafter; the highest levels were found at the beginning of the contact period: this means that the rate of absorption and diffusion into the plasma is rapidly overtaken by the rate of disappearance of the substance from the plasma.

Assay of the saliva and rinsing fluid expelled at 3½ min revealed that 25 to 40% of the dose of nitroglycerin given was not absorbed; surprisingly some metabolites, the 1,2- and 1,3-glyceryl dinitrates were already present in fair amounts in this fluid.

Finally, although the study was not planned for measurement of cardiovascular effects, the increase of heart rate after the different doses was noted; this increase started around the second minute; with the higher doses it was more pronounced, but, even then, short lasting; plasma levels at the moment the heart rate was back to control values after giving the high doses, were more elevated than plasma levels during the increase of heart rate seen with lower doses.

We think that the plasma levels of nitroglycerin in man after buccal administration can serve as reference values for further work on the problem of retard preparations and of the so-called long acting nitrates.

*J. F. and C. Heymans Institute of Pharmacology,
University of Ghent Medical School,
Ghent, Belgium.*

M. G. BOGAERT
M.-T. ROSSEEL

June 1, 1972

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