Notes and Miscellanea

The Plasma Content and Excretion of Catecholamines in Nitroglycerine Workers

J. HÄGGENDAL, G. JOHNSON, and R. P. LUND

From the Department of Pharmacology, University of Göteborg, and AB Bofors Nobelkrut, Bofors, Sweden

Explosives workers and patients often show symptoms of headache, postural weakness, dizziness, palpitations of the heart, sweating, etc. after exposure to nitrites or alkyl nitrates (Melville, 1965). These symptoms may be ascribed largely to the cardiovascular effects of these agents. Nitrites and alkyl nitrates have a powerful vasodilator action, predominantly on capacitance vessels, mainly the veins, and a comparatively weak action on resistance vessels, predominantly the arterioles and the small veins (Åblad and Mellander, 1963; Åblad, 1963; Johnson, Henning, and Åblad, 1965).

As a rule tolerance is developed to these agents within a week. Thereafter such symptoms disappear or become rather mild. The mechanism of the development of tolerance has not been clarified. As the activity of the sympathetic nervous system appears to be important for the smooth muscle tone of the capacitance vessels (Mellander, 1960), it may be supposed that an increased activity of the sympathetic nervous system contributes to the development of tolerance. It was, therefore, of interest to study the amounts of endogenous noradrenaline (NA) excreted by workers who had developed tolerance to nitroglycerine. Increased impulse activity in the sympathetic nervous system may in some cases (Carlsson, Folkow, and Häggendal, 1964) give rise to increased amounts of NA in the urine and blood plasma (von Euler, 1956; Vendsalu, 1960).

Materials and Methods

Determinations of the urinary excretion of NA and adrenaline (A) were performed on 20 workers in explosives production (exposed persons) and a control group of 15 persons (6 clerks, 3 foremen, and 6 workers). The ages varied in about the same way in the two groups

(range 25-60 years). All persons were healthy. The urine was collected for 24 hours from Thursday morning until Friday morning during a normal working week.

The amounts of NA and A were also determined in the plasma of five workers exposed to nitroglycerine and six non-exposed workers. The blood samples were taken during a normal working day after the subjects had rested for about half an hour in a recumbent position.

The catecholamines were determined fluorimetrically by the trihydroxyindole method (Bertler, Carlsson, and Rosengren, 1958; Häggendal, 1963).

Results

The urinary excretion of NA and A was not significantly different between the exposed group and the non-exposed. The sum of NA and A per 24 hours was 60.5 ± 5.2 μ g. and 49.1 ± 3.9 μ g. (mean $\pm$ S.E.M.) respectively. No difference was found between the two groups with respect to the urinary excretion of A (approximately 10% of the total amount of A and NA). In the exposed group, 9 workers out of 20 excreted 60 μ g. or more of NA, while in the control group 3 out of 15 persons excreted 60 μ g. or more of this catecholamine.

The concentration of NA in plasma was 0.4 ± 0.20 μ g. per litre plasma in the exposed group. One person in this group had a value of 0.6 μ g. NA per litre plasma. The corresponding mean value for the non-exposed group was 0.4 ± 0.23 μ g. In this group also one worker had a value of 0.6 μ g. No significant amounts of A could be detected in the plasma of either group.

Comments

The mean urinary excretion of NA and A in the two groups appears to be within the range for normal values (von Euler, 1956). The fact that 9 cases in the exposed group of 20 workers excreted more than

60 μ g. NA per 24 hours compared to three out of 15 in the control group might indicate an increased release of NA on exposure to nitroglycerine in some workers.

However, this increased release may be explained by factors other than exposure to nitroglycerine. Thus the urinary volumes were greater in those with the highest excretion of NA than in the others. There appear to be conflicting reports about the effect of diuresis on the excretion of catecholamines (Kärki, 1956; Schaepdryver and Leroy, 1961). According to the latter authors, there is a clearcut parallelism between urine volume and NA-A excretion in the urine. The increased urinary excretion of catecholamines in some exposed workers may also be due to physical stress factors, such as a warm working milieu and heavy physical work.

The interpretation that the increased urinary excretion of NA in some workers may be ascribed to factors other than exposure to nitroglycerine is supported by the plasma analysis of NA. The above-mentioned physical stress factors appear to be eliminated in the studies on the NA levels in plasma in which there was no difference in the NA values between the two groups.

The present results give no clearcut support for the hypothesis that the activity in the sympathetic nervous system, as reflected in the amounts of NA in the plasma and the excreted NA, is markedly increased in persons who have developed tolerance to nitroglycerine.

On the other hand, the results do not exclude the possibility that the sympathetic nervous system is involved in the development of tolerance to nitroglycerine. An increased impulse frequency in the sympathetic nervous system may not necessarily be reflected in an increased plasma level or an increased urinary excretion of NA. Other factors, such as the neuronal reuptake of the released NA, may be changed and conceal an increased impulse frequency (Folkow, Häggendal, and Lisander, 1967).

Changes of these local inactivating mechanisms for released transmitter may cause the increased sensitivity to adrenaline, reported by Yoshikawa (1965), to occur after nitroglycol withdrawal in

nitroglycol pretreated mice.

The study was supported by the Swedish Medical Research Council (B67-14X-166-03 and B68-14X-166-04) and by Läkemedelsindustriföreningen, Stockholm, Sweden. The authors are indebted to Miss Inger Eriksson for technical assistance.

REFERENCES

- Åblad, B. (1963). A study of the mechanism of the hemodynamic effects of hydralazine in man. *Acta pharmacol. (Kbh.)*, **20**, Suppl. 1.
- , and Mellander, S. (1963). Comparative effects of hydralazine, sodium nitrite and acetylcholine on resistance and capacitance blood vessels and capillary filtration in skeletal muscle in the cat. *Acta physiol. scand.*, **58**, 319-329.
- Bertler, Å., Carlsson, A., and Rosengren, E. (1958). A method for the fluorimetric determination of adrenaline and noradrenaline in tissues. *Ibid.*, **44**, 273-292.
- Carlsson, A., Folkow, B., and Häggendal, J. (1964). Some factors influencing the release of noradrenaline into the blood following sympathetic stimulation. *Life Sci.*, **3**, 1335-1341.
- Euler, U. S. von (1956). *Noradrenaline*. Thomas, Springfield, Illinois.
- Folkow, B., Häggendal, J., and Lisander, B. (1967). Extent of release and elimination of noradrenaline at peripheral adrenergic nerve terminals. *Acta physiol. scand. Suppl.* 307.
- Häggendal, J. (1963). An improved method for fluorimetric determination of small amounts of adrenaline and noradrenaline in plasma and tissues. *Ibid.*, **59**, 242-254.
- Johnsson, G., Henning, M., and Åblad, B. (1965). Rate of onset of vasodilator effect of glyceryl trinitrate, propatyl nitrate and erythrityl tetranitrate in man. *Scand. J. clin. Lab. Invest.*, **17**, 600-606.
- Kärki, N. T. (1956). The urinary excretion of noradrenaline and adrenaline in different age groups, its diurnal variation and the effect of muscular work on it. *Acta physiol. scand.*, **39**, Suppl. 132.
- Mellander, S. (1960). Comparative studies on the adrenergic neurohormonal control of resistance and capacitance blood vessels in the cat. *Ibid.*, **50**, Suppl. 176.
- Melville, K. I. (1965). Coronary vasodilators, in *Drill's Pharmacology in Medicine*, 3rd ed. Ed. DiPalma, J. R. pp. 594-623. McGraw-Hill, New York.
- Schaepdryver, A. F. de, and Leroy, J. G. (1961). Urine volume and catecholamine excretion in man. *Acta cardiol. (Brux.)*, **16**, 631-638.
- Vendsalu, A. (1960). Studies on adrenaline and noradrenaline in human plasma. *Acta physiol. scand.*, **49**, Suppl. 173.
- Yoshikawa, H. (1965). Changes of sensitivity to adrenaline on the nitroglycol poisoned mice. *Industr. Hlth (Kawasaki)*, **3**, 86-90.